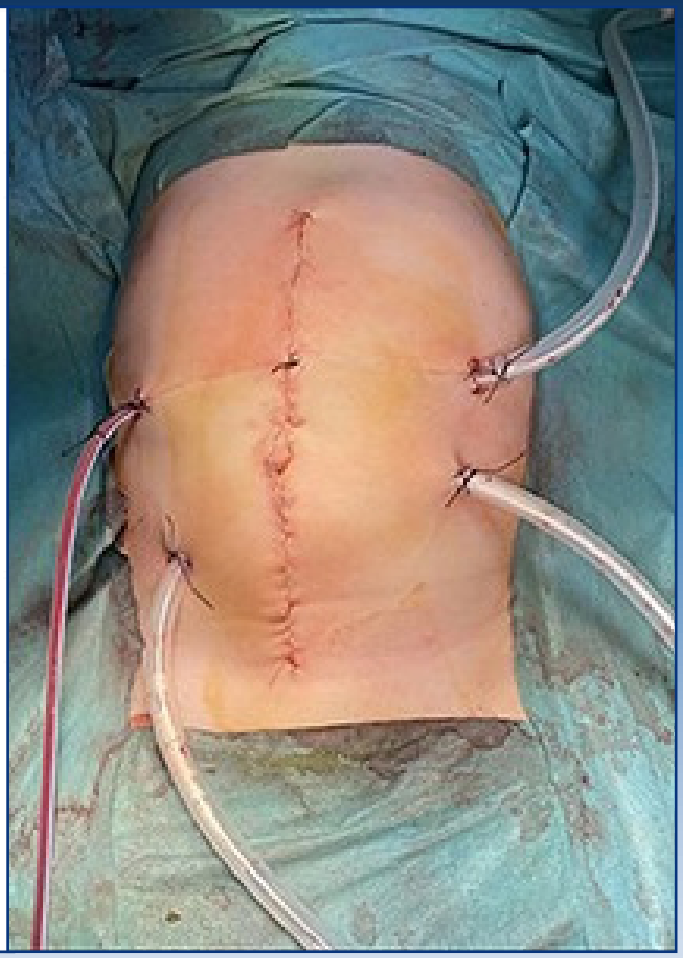
1917 2025 108

RHODE ISLAND MEDICAL JOURNAL



SPECIAL SECTION

UPDATES *in* SURGICAL ONCOLOGY

GUEST EDITOR: STEVE KWON, MD, MPH, MBA, FACS, FSSO

JULY 2025 VOLUME 108 • NUMBER 7 ISSN 2327-2228

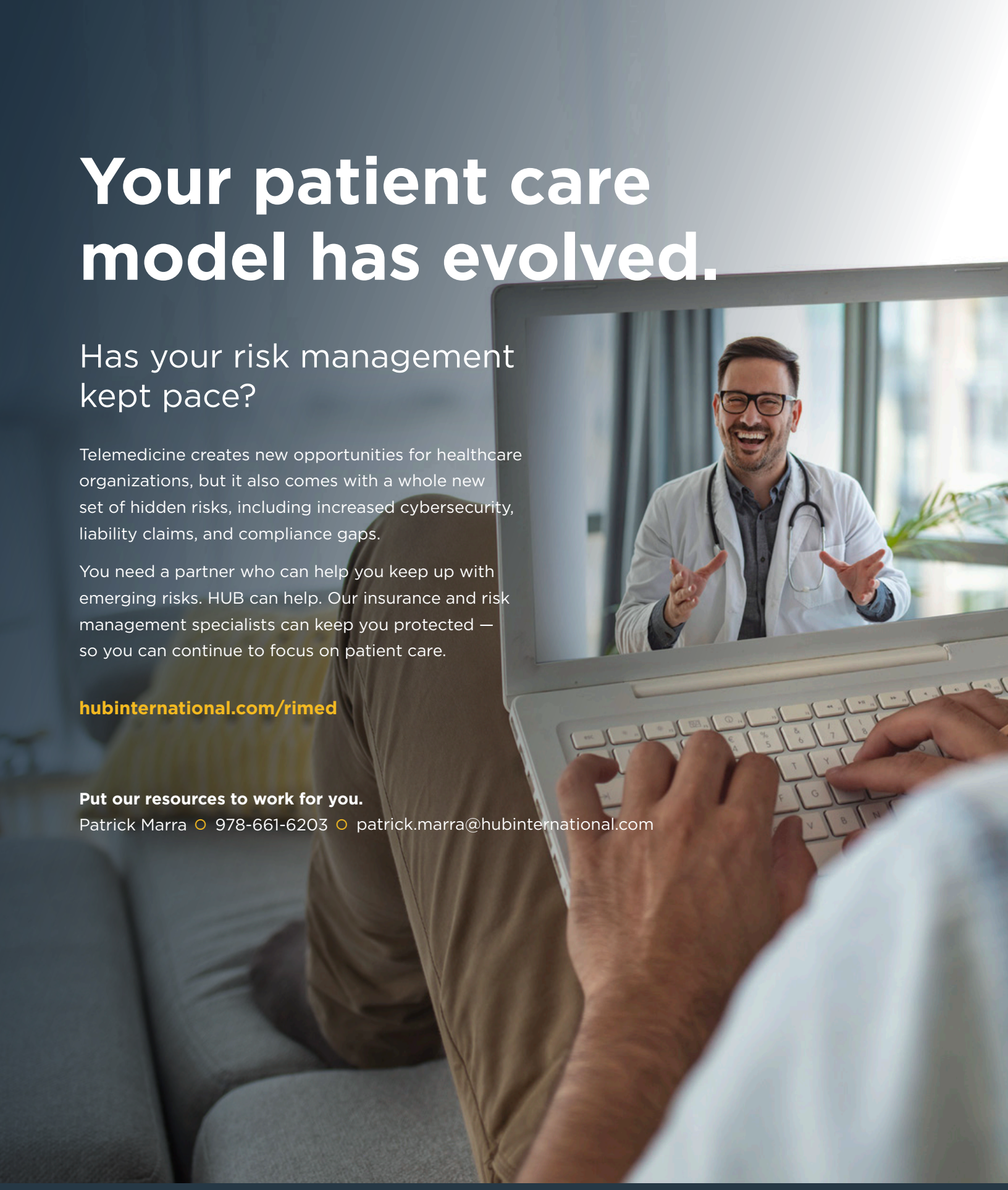
Your patient care model has evolved.

Has your risk management kept pace?

Telemedicine creates new opportunities for healthcare organizations, but it also comes with a whole new set of hidden risks, including increased cybersecurity, liability claims, and compliance gaps.

You need a partner who can help you keep up with emerging risks. HUB can help. Our insurance and risk management specialists can keep you protected — so you can continue to focus on patient care.

hubinternational.com/rimed



Put our resources to work for you.

Patrick Marra ○ 978-661-6203 ○ patrick.marra@hubinternational.com

HUB

Risk & Insurance | Employee Benefits | Retirement & Private Wealth

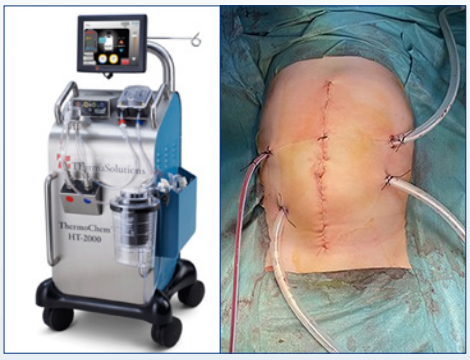
RHODE ISLAND
MEDICAL JOURNAL

Steve Kwon, MD, MPH

SPECIAL SECTION

Updates in Surgical Oncology

STEVE KWON, MD, MPH, MBA, FACS, FSSO
GUEST EDITOR



Cover images are from theme article "Current Applications of Intraperitoneal Chemotherapy" and show HIPEC machine (from ThermaSolutions) and intraoperative set-up of HIPEC instillation – closed abdomen technique.

JULY 2025
VOLUME 108 • NUMBER 7

RHODE ISLAND MEDICAL JOURNAL

FOLLOW RIMJ

RHODE ISLAND MEDICAL JOURNAL (USPS 464-820), a monthly publication, is owned and published by the Rhode Island Medical Society, 225 Dyer Street, 2nd Floor, Providence RI 02903, 401-331-3207. All rights reserved. ISSN 2327-2228. Published articles represent opinions of the authors and do not necessarily reflect the official policy of the Rhode Island Medical Society, unless clearly specified. Advertisements do not imply sponsorship or endorsement by the Rhode Island Medical Society.

IMAGES IN MEDICINE

RESEARCH STUDIES

PUBLIC HEALTH

RHODE ISLAND MEDICAL JOURNAL

IN THE NEWS

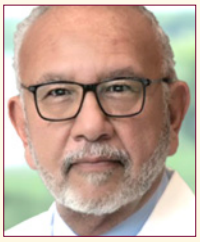

K. MacCallum, MD


Y. Singh, PhD


N. McKinney, MD


M. Viveiros, DNP


J. Assif, MD


N.J. Espat, MD


S. Kwon, MD


E. Renaud, MD

PEOPLE/PLACES

OBITUARIES

Favorite
Healthcare Staffing

Rhode Island's Medical Staffing Experts

Favorite Healthcare Staffing provides a comprehensive range of staffing services at preferred pricing to RIMS members. Call today to see why we are the favorite choice of healthcare professionals and physician practices across the US!

401.354.7115

MedicalStaffing@FavoriteStaffing.com

Favorite Healthcare Staffing is a Valued Sponsor of the Rhode Island Medical Society

AA / EOE / M / F / V / D

Introduction: Updates in Surgical Oncology

STEVE KWON, MD, MPH, MBA, FACS, FSSO
GUEST EDITOR

The field of surgical oncology has undergone transformative evolution in the past decade, reflecting the impact of multidisciplinary cancer research and redefinement of the possibilities of surgical care. Procedures have become less invasive, safer, and more accurate with new technology such as robotic approaches and expanding uses of minimally invasive surgeries. In terms of management, we are understanding how to de-escalate surgical oncology care. There is an understanding that more may not be necessarily better with the rise of modern, powerful therapies such as immunotherapies. For example, cancer types such as rectal cancer are now being treated with chemotherapy and radiation alone if these therapies are able to achieve complete pathological responses.[1] At the same time, we are also understanding when to escalate surgical oncology care. For example, the use of regional therapies in advanced, unresectable cancers have allowed expanding opportunities to convert patients who were once deemed inoperable and uncurable over to resectable and curable states.[2,3] With this special issue in surgical oncology, we hope to share some of the advances and evolving treatment options for patients in the state of Rhode Island. Below is a quick synopsis of what is to come in this special edition on updates in surgical oncology.

Once considered to be systemic disease, colorectal liver metastases have evolved to be considered potentially curable disease. Local liver therapy in the form of liver resection has resulted in 10-year survival of 22 to 26% in the late 1990s to early 2000s.[4,5] Survival rates of colorectal metastases continues to improve with one estimate demonstrating median overall survival of 22.6 months for patients diagnosed between 2004 and 2012 to 32.4 months for those diagnosed between 2016 and 2019, helped by powerful modern chemotherapy and the rise of immunotherapy.[6] With the ability to achieve longer survival rates, multiple liver-directed therapies have been highlighted as an adjunct to systemic therapy. Numerous options now exist for patients, with opportunity to personalize treatments to optimize every patient's individual outcome. To help us grasp an understanding of various treatment options, **CROCKER ET AL** cover a wide range of treatment armamentarium available in the treatment of patients with colorectal liver metastases. These range from trans-arterial chemotherapy, trans-arterial radioembolization, thermal tumor ablations, and hepatic artery infusion chemotherapy pumps. The authors highlight data behind each of these modalities and certain indications for their use, and help the readers to appreciate the therapies that are available for patients in Rhode Island. Another regional therapy utilization in surgical oncology is with the surgical management of peritoneal carcinomatosis – intraperitoneal chemotherapy. Peritoneal carcinomatosis remains a challenging pathology with poor patient prognosis and symptoms. Intraperitoneal chemotherapy has been around since 1950s but it is underutilized due to lack of awareness and limited access to hyperthermic intraperitoneal chemotherapy (HIPEC) experts.[7] With the treatment being readily available in Rhode Island, **WILSON ET AL** provide a nice overview of the treatment, appropriate patients who may benefit from the treatment, and its impact on survival and patients' quality of life to improve our awareness and consideration of this important treatment modality.

Then we turn to three manuscripts on the opposite spectrum to highlight new technologies that have allowed for less invasive approaches. A minimally invasive surgery (MIS) approach is increasingly utilized for liver surgeries. With the robotic platform, further growth in MIS for liver is anticipated. **TALUKDER ET AL** discuss some of the potential benefits of the MIS approach for patients with primary and secondary liver malignancies, including its association with lower complications, shorter length of stay, and perioperative mortality that has dropped below 2% in modern times. An overview of the technologies that has helped with the safety profile of liver surgeries are discussed, including the use of Indocyanine Green and intraoperative ultrasound to delineate tumor and to facilitate parenchymal-sparing resections, which has helped decrease the rate of post-hepatectomy liver failure and postoperative recovery. Ablation techniques including novel Histotripsy treatment are also discussed to round out the authors' discussion on MIS approach to primary and secondary liver cancers. This theme of minimally invasive approaches is extended into pancreatic surgeries by **WILSON ET AL**. The authors provide a comprehensive review addressing the indications for pancreatic surgeries, traditional techniques involved in pancreatic surgeries and discuss the rise of minimally invasive pancreatic surgeries as well as other emerging techniques and exciting technological developments in the field of pancreatic surgery.

Lastly, **LI ET AL** introduce an emerging technology to treat benign symptomatic thyroid nodules. Radiofrequency ablation (RFA) may help shift some surgical resection to minimally invasive, low-risk alternative. RFA has been shown to be a cost-effective alternative with excellent results in reducing thyroid nodule volume, improving symptoms, and cosmetic appearance. The authors nicely outline patient selection criteria and one's eligibility for this procedure. The special edition on surgical oncology ends with providing an interesting epidemiology of cancer in Rhode Island. Using Cholangiocarcinoma as a case study, **LIGHTFOOT ET AL** provide a nice epidemiological overview of cancer risks in Rhode Island and provide an interesting insights into the relationship between environmental factors in Rhode Island and cancer. This article highlights growing interest in recognizing cancer as a public health and environmental issue. It also highlights oncology as a true multidisciplinary field where surgical oncology is one component of many others. As the field of surgical oncology evolves, it is evolving together with other cross-linked disciplines.

The ancient Greek philosopher, Heraclitus, famously stated, "there is nothing permanent except change." The field of surgical oncology is constantly transforming, but the fundamental goal remains true – we continuously seek to find new and innovative ways to address cancer by physical intervention.

References

1. Williams H, Lee C, Garcia-Aguilar J. Nonoperative management of rectal cancer. *Front Oncol*. 2024;14:1477510. doi:10.3389/fonc.2024.1477510
2. Berger Y, Schuitevoerder D, Vining CC, et al. Novel Application of Iterative Hyperthermic Intraperitoneal Chemotherapy for Unresectable Peritoneal Metastases from High-Grade Appendiceal Ex-Goblet Adenocarcinoma. *Ann Surg Oncol*. Mar 2021;28(3):1777-1785. doi:10.1245/s10434-020-09064-7
3. Kemeny NE, Melendez FD, Capanu M, et al. Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma. *J Clin Oncol*. Jul 20 2009;27(21):3465-71. doi:10.1200/JCO.2008.20.1301
4. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg*. Jun 2002;235(6):759-66. doi:10.1097/00000658-200206000-00002
5. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg*. Sep 1999;230(3):309-18; discussion 318-21. doi:10.1097/00000658-199909000-00004
6. Zeineddine FA, Zeineddine MA, Yousef A, et al. Survival improvement for patients with metastatic colorectal cancer over twenty years. *NPJ Precis Oncol*. Feb 13 2023;7(1):16. doi:10.1038/s41698-023-00353-4
7. Bernaiche T, Emery E, Bijelic L. Practice patterns, attitudes, and knowledge among physicians regarding cytoreductive surgery and HIPEC for patients with peritoneal metastases. *Pleura Peritoneum*. Mar 1 2018;3(1):20170025. doi:10.1515/pp-2017-0025

Guest Editor

Steve Kwon, MD, MPH, MBA, FACS, FSSO, Boston University; Roger Williams Medical Center, Providence, RI.

Correspondence

steve.kwon@chartercare.org

Regional Hepatic Therapies for Colorectal Hepatic Metastases

ANDREW B. CROCKER, MD; MUNYA H. TALUKDER, MD; MOHAMMAD S. ALI, MD; ABDUL SAIED CALVINO, MD, MPH; PONNANDAI SOMASUNDAR, MD, FACS; N. JOSEPH ESPAT, MD, MS, FSSO, FACS

ABSTRACT

The modern era of hepatic resection began with the first published report on "formal" right hemi-hepatectomy by Jean Louis Lortat–Jacob in France in 1952.[1] Advanced imaging has enabled improved patient selection for potentially curative resection.[2] Dramatic clinical and technical innovations over the last several decades have resulted in >50% five-year survival for patients undergoing resection; however, only about 25% patients with colorectal hepatic metastases (CRHM) will be candidates for operation.[3] Given this modest rate of resectability, most patients will require a combination of systemic and local non-surgical therapies

In this patient population, besides systemic chemotherapy, treatment modalities collectively termed "regional hepatic therapies (RHT)" may be employed. RHT include trans-arterial chemotherapy, hepatic artery infusion (HAI) pumps, trans-arterial radio-embolization (TARE) with Yttrium-90 (Y-90) and thermal tumor ablation using radiofrequency ablation (RFA) or microwave ablation (MWA). [4]

In this review, we introduce RHT and discuss their utility in the modern day.

KEYWORDS: systemic chemotherapy; hepatic resection; hepatic artery infusion; trans-arterial embolization; thermal tumor ablation

INTRODUCTION

Surgical resection is the gold standard for the potential curative treatment of CRHM, but optimal patient selection continues to evolve. While there are few generally accepted guidelines, the consensus is that absolute contraindications to resection include: extensive extrahepatic disease, involvement of more than 70% or six segments of liver, tumor involvement of major hepatic artery, major bile ducts or main portal veins or co-morbidities preventing surgery.[4] Barring these contraindications, operative resection in the management of colorectal hepatic metastases should be routinely considered and evaluation by experienced hepatic surgeons is the standard of care.

For patients with resectable CRHM, there must be the potential to achieve complete resection with negative margins without evidence of extrahepatic disease, which is essential for survival.[5] Patients with borderline resectable disease may not be initially deemed operable due to inadequate liver reserve, high risk of positive margin, or prior metastatic disease that is no longer visible. These patients along with patients with advanced surgically untreatable liver dominant disease will benefit from systemic therapy and non-operative regional treatment adjuncts.[6-7] In some patients these non-surgical therapies may also improve resectability.

There is a wealth of historical data suggesting the utility and effectiveness of hepatic resection in colorectal liver metastases. Collectively, over time, multiple studies reviewing surgical resection outcome for CRHM have demonstrated overall survival with reproducible five-year survival metrics above 50%.[8-12]

SYSTEMIC CHEMOTHERAPY

Systemic chemotherapy is an important treatment modality that can be used as adjuvant to resection, in a neoadjuvant manner for potentially resectable, and as primary therapy for unresectable CRHM.

Prior the FOLFOX era (2008), the chemotherapy agent most often employed was 5-Flourouracil (5-FU). In the preceding 20 years to FOLFOX, the extent of progress had been the advancement from 5-FU + Levamisole to 5 FU + Leucovorin. Rapidly after the introduction of FOLFOX the advent of specific anti-angiogenic therapies led to the now explosive era of targeted/immunotherapies.[13-16] These modern chemotherapy ± immunotherapy regimens have demonstrated remarkably improved outcomes for resectable and non-resectable CRHM, and median survival with 5-FU based regimens has dramatically improved with time.[17-18]

Conceptually, patients that can undergo curative resection and patients that are only candidates for systemic chemotherapy, represent the treatment extremes of this population. Most patients will be in-between, and it is for these patients RHT have the potential utility.

REGIONAL HEPATIC THERAPIES

Regional hepatic therapies (RHT) can be broadly organized into nonarterial, arterial, and ablative modalities.

Non-arterial modalities include radiosurgery and intense modulated radiation therapy (IMRT) or image-guided radiation therapy (IGRT). Arterial regional hepatic therapies include non-embolic treatment such as the hepatic artery infusion pumps (HAI) or embolic treatment such as Y-90 trans-arterial radioembolization (TARE). Thermal ablative modalities include hot-thermal modalities such as RFA and MWA or cold-thermal modality such as cryoablation (not discussed, due to limited modern use).

Fundamental to arterial-based approaches was the description in the 1970s that tumors in the liver >3mm derive their blood supply from the hepatic artery and not the portal vein.[19] Thus, increased delivery and concentration of chemotherapy is achieved by arterial infusion compared to systemic venous infusion and this is the principle for hepatic artery infusion pumps.

Next, trans-arterial radioembolization with yttrium 90 utilizes the arterial route to deliver targeted brachytherapy and internal tumor embolization.[20] CRHM are vascularized in peripheral neo-angiogenic arcades with central necrosis, thus traditional embolization ± chemotherapy is of limited use. Additionally, the known susceptibility of hepatic parenchyma to radiation requires a focused and defined delivery of radiation to tumor while sparing normal parenchyma.

Last, hot-thermal ablation relies on heat induction by electromagnetic resonance to achieve protein denaturation progressing to tumor coagulative necrosis.[21] Radiofrequency ablation (RFA) and Microwave ablation (MWA) are generally grouped together; however, the mechanism for the heat generation is distinct and RFA is more susceptible to incomplete tumor destruction due to energy loss to nearby structures causing a "heat-sink". MWA ablation is the newer modality and likely due to the efficiency in heat delivery has become the more commonly used modality.[22]

Hepatic Artery Infusion (HAI)

HAI pumps are subdermally implanted specialized infusion pumps that deliver chemotherapy through a surgically placed catheter passing retrograde from the gastroduodenal artery to the proper hepatic arterial circulation. In this way, HAI takes advantage of both liver metabolism and tumor blood supply.[23] The liver metabolizes certain drugs in a "first pass" effect, i.e. 5-FU to floxuridine.[24] This leads to high intrahepatic concentrations with minimal systemic toxicity, which makes drugs with short half-lives such as Floxuridine (FUDR) useful. 5-FU specifically demonstrated up to 99% extraction by the liver during first-pass metabolism.[25]

HAI has various roles; it can be used for initially unresectable colorectal hepatic metastases to potentially convert to resectability, as adjuvant liver-directed therapy post liver resection or as liver directed therapy in combination with systemic therapy for unresectable otherwise untreatable disease.

In a prospective phase II study, 33 of 64 (52%) patients were reported to have conversion to resection after receiving hepatic artery infusion FUDR with modern systemic chemotherapy.[26] Conversion to resection was associated with long-term survival, with a five-year OS for resected disease at 63.3% compared with 12.5% for patients who did not undergo resection.[26] Overall, studies support the use of HAI to increase the number of patients who are eligible for resection, which is associated with longer survival.

HAI can also be used as an adjuvant therapy after liver resection. A retrospective study of 125 patients treated between 2000 and 2005 with adjuvant HAI with FUDR and concurrent systemic chemotherapy including 5-FU plus oxaliplatin or irinotecan found that patients who received HAI with FUDR with systemic chemotherapy demonstrated improved OS and hepatic PFS compared with those who received systemic therapy alone.[27] The strongest evidence for adjuvant HAI is from the Memorial Sloan Kettering Cancer Center (MSKCC) group who reported results from 2,368 patients with consecutive colorectal hepatic metastases resections who received modern systemic chemotherapy, 785 of which also had adjuvant HAI with FUDR. Despite a higher disease burden, patients who received combined therapy had a longer median OS of 67 months compared with 44 months for those who were treated with adjuvant systemic chemotherapy alone ($p < 0.01$).[28] This survival benefit persisted as the ten-year OS was 38.0% in the HAI/systemic therapy group compared with 23.8% in the systemic therapy–alone group.

In 2006, a multi-institutional study of HAI was reported by the Cancer and Leukemia Group B for patients with unresectable otherwise untreatable colorectal hepatic metastases. A total of 135 patients with hepatic metastases were randomly assigned to receive HAI FUDR/leucovorin/dexamethasone compared with 5-FU/leucovorin. OS was favored with HAI with FUDR at 24.4 months versus 20.0 months for systemic therapy ($p = .0034$).[29]

It is worth noting that there is strong literature going back to the early 1990s for the survival benefit of HAI.[30] However, in the era of 5-FU there remain few specialized centers with dedicated HAI programs. There has been renewed interest in this modality in the last few years as modern systemic agents have been proven effective. As more centers adopt HAI programs the use of this treatment option will become increasingly common. Established centers continue to demonstrate viability of this approach with robust clinical studies, but an individualized approach will be necessary as not all centers may have HAI programs at their disposal. When available, HAI should be considered for patients with CRHM.

Transarterial Radioembolization (TARE)

TARE is a catheter-based intra-arterial technique that focally delivers a high radiation dose using β-radiator Yittrium-90 (Y-90) into hepatic tumors; this results in tumor necrosis and fibrosis. TARE should be considered for patients with

colorectal hepatic metastases with liver-limited disease that have failed to respond to systemic chemotherapeutic options or are not candidates for resection. The Y-90 TARE concept dates to the 1970s when Y-90 TARE was initially used to salvage patients with CRHM being treated with HAIP that had progressed though HAIP therapy. Since then, TARE was shown to be beneficial in conjunction with systemic chemotherapy in the pre-FOLFOX era. In a phase III randomized controlled clinical trial of 44 patients with chemorefractory disease who were treated with 5-FU or TARE/5-FU, patients who received the combined TARE/5-FU demonstrated longer time to tumor progression (median, 4.5 months vs. 2.1 months; p = .03) and longer time to liver progression (median, 5.5 months vs. 2.1 months; p = .003).[20]

In the modern era of FOLFOX, the use of TARE for patients with treatment-naïve colorectal hepatic metastases has been evaluated in three large randomized controlled trials. In the SIRFLOX trial, van Hazel et al, randomly assigned 530 patients with treatment-naïve disease to FOLFOX versus TARE/FOLFOX with or without bevacizumab.[31] Although TARE/FOLFOX did not improve PFS (median, 10.7 months vs. 10.2 months; p = .43), median liver PFS was longer in the TARE trial arm (20.5 months vs. 12.6 months; p = .002). The combined results of the three phase III trials, SIRFLOX, FOXFIRE, and FOXFIRE Global, which evaluated the effectiveness of TARE/FOLFOX as first-line treatment for 1,103 patients with treatment-naïve colorectal liver metastases, did not note prolonged OS compared with FOLFOX alone (median OS, 22.6 months vs. 23.3 months; p = .61).[32] However, subgroup analyses suggested that selected patients might benefit from TARE. These analyses highlight the necessity for optimized patient selection to maximize the clinical effectiveness of TARE and to provide individualized treatment schemes.

Thermal Ablation

Thermal tumor ablation techniques (RFA/MWA) induce tumor cell death through frictional heating resulting in protein denaturation and coagulation necrosis. Ablation can be considered for patients with CRHM that are deemed unresectable or as a combined approach with resection. It is preferred for patients with less than three lesions, each with a diameter less than 3 cm.[33] While it may be offered independently, it can also be utilized alongside surgical resection in patients with small or low volume metastatic burden isolated to the liver. Ablation may be done in the open, laparoscopic or image-guided percutaneous setting. Percutaneous ablation with image guidance is most frequently performed for patients with recurrence after hepatectomy. In all cases where thermal ablation is planned, all metastatic disease sites must be feasible and accessible for ablation with encompassed treatment margins. The choice of laparoscopic versus percutaneous image guided thermal ablation depends on practical factors related to tumor size and location for accessibility.

Several studies have been published over the last two decades demonstrating the effectiveness and safety of thermal ablation for CRHM. One phase II trial randomly assigned 119 patients with CRHM to systemic therapy versus radiofrequency ablation plus systemic therapy with or without surgical resection. Longer OS was reported for the combination treatment (HR, 0.58; 95% CI, 0.38–0.88; p = .01).[34] Associated five-year OS rates were 43.1% versus 30.3%, with a median OS of 45.6 months versus 40.5 months. Wang et al, described excellent outcomes in 115 patients with CRHM who underwent percutaneous ultrasound-guided microwave ablation; three-year OS was 78.7% and the three-year recurrence rate was 59.3%.[35]

Both RFA and MWA show comparable technical success rates, outcomes, and safety in patients with CRHM.[36] However, MWA demonstrates a technical advantage over RFA because of a reduced heat-sink effect.[37]

SUMMARY

Surgical hepatic resection with clear margins has been and remains the gold standard for the potentially curative treatment of CRHM. However, modest rates of surgical resectability require a multidisciplinary team approach employing systemic chemotherapy and the various regional hepatic therapies.

There is a consistent theme to this disease; there is no one independent "magic bullet". While resection is the gold standard for potential cure there is still the need for adjuvant systemic chemotherapy ± immunotherapy. The recurring theme is that a combination of modalities is required to achieve the best possible outcome. Considering the well-documented historical experiences with combined modalities, the evidence is clear that treatment must be individualized and that patients need to have a care team that is aware and knowledgeable in the various options that are available.

A care team must have expertise in the total assessment of the patient to inclusively and collaboratively recommend treatment. Modern treatment strategy necessitates a patient-centered approach to fully optimize clinical options and outcomes.

References

1. Fineberg C, Goldburgh WP, Templeton JY. Right hepatic lobectomy for primary carcinoma of the liver. Ann Surg. 1956 Nov;144(5):881-92. doi: 10.1097/00000658-195611000-00013. PMID: 13373274; PMCID: PMC1465280.
2. Bipat S, van Leeuwen MS, Comans EF, Pijl ME, Bossuyt PM, Zwinderman AH, Stoker J. Colorectal liver metastases: CT, MR imaging, and PET for diagnosis--meta-analysis. Radiology. 2005 Oct;237(1):123-31. doi: 10.1148/radiol.2371042060. Epub 2005 Aug 11. PMID: 16100087.
3. Su YM, Liu W, Yan XL, Wang LJ, Liu M, Wang HW, Jin KM, Bao Q, Wang K, Li J, Xu D, Xing BC. Five-year survival post hepatectomy for colorectal liver metastases in a real-world Chinese

cohort: Recurrence patterns and prediction for potential cure. Cancer Med. 2023 Apr;12(8):9559-9569. doi: 10.1002/cam4.5732. Epub 2023 Feb 27. PMID: 36846977; PMCID: PMC10166917.

4. Pwint TP, Midgley R, Kerr DJ. Regional hepatic chemotherapies in the treatment of colorectal cancer metastases to the liver. Semin Oncol. 2010 Apr;37(2):149-59. doi: 10.1053/j.seminoncol.2010.03.005. PMID: 20494707.
5. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A, Diaz-Rubio E, Douillard JY, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V, Hoff P, Köhne CH, Labianca R, Laurent-Puig P, Ma B, Maughan T, Muro K, Normanno N, Österlund P, Oyen WJ, Papamichael D, Pentheroudakis G, Pfeiffer P, Price TJ, Punt C, Ricke J, Roth A, Salazar R, Scheithauer W, Schmoll HJ, Tabernero J, Taïeb J, Tejpar S, Wasan H, Yoshino T, Zaanan A, Arnold D. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016 Aug;27(8):1386-422. doi: 10.1093/annonc/mdw235. Epub 2016 Jul 5. PMID: 27380959.
6. Shindoh J, Tzeng CW, Aloia TA, Curley SA, Zimmitti G, Wei SH, Huang SY, Mahvash A, Gupta S, Wallace MJ, Vauthey JN. Optimal future liver remnant in patients treated with extensive preoperative chemotherapy for colorectal liver metastases. Ann Surg Oncol. 2013 Aug;20(8):2493-500. doi: 10.1245/s10434-012-2864-7. Epub 2013 Feb 3. PMID: 23377564; PMCID: PMC3855465.
7. Kishi Y, Abdalla EK, Chun YS, Zorzi D, Madoff DC, Wallace MJ, Curley SA, Vauthey JN. Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. Ann Surg. 2009 Oct;250(4):540-8. doi: 10.1097/SLA.0b013e3181b674df. PMID: 19730239.
8. Fernandez FG, Drebin JA, Linehan DC, Dehdashti F, Siegel BA, Strasberg SM. Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). Ann Surg. 2004 Sep;240(3):438-47; discussion 447-50. doi: 10.1097/01.sla.0000138076.72547.b1. PMID: 15319715; PMCID: PMC1356434.
9. Choti MA, Sitzmann JV, Tiburi MF, Sumetchotimetha W, Rangsin R, Schulick RD, Lillemoe KD, Yeo CJ, Cameron JL. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg. 2002 Jun;235(6):759-66. doi: 10.1097/00000658-200206000-00002. PMID: 12035031; PMCID: PMC1422504.
10. Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR, Hess K, Curley SA. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg. 2004 Jun;239(6):818-25; discussion 825-7. doi: 10.1097/01.sla.0000128305.90650.71. PMID: 15166961; PMCID: PMC1356290.
11. Pawlik TM, Scoggins CR, Zorzi D, Abdalla EK, Andres A, Eng C, Curley SA, Loyer EM, Muratore A, Mentha G, Capussotti L, Vauthey JN. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg. 2005 May;241(5):715-22, discussion 722-4. doi: 10.1097/01.sla.0000160703.75808.7d. PMID: 15849507; PMCID: PMC1357126.
12. Miller G, Biernacki P, Kemeny NE, Gonen M, Downey R, Jarnagin WR, D'Angelica M, Fong Y, Blumgart LH, DeMatteo RP. Outcomes after resection of synchronous or metachronous hepatic and pulmonary colorectal metastases. J Am Coll Surg. 2007 Aug;205(2):231-8. doi: 10.1016/j.jamcollsurg.2007.04.039. Epub 2007 Jun 27. PMID: 17660069.
13. Siriwardena AK, Serrablo A, Fretland ÅA, Wigmore SJ, Ramia-Angel JM, Malik HZ, Stättner S, Søreide K, Zmora O, Meijerink M, Kartalis N, Lesurtel M, Verhoef K, Balakrishnan A, Gruenberger T, Jonas E, Devar J, Jamdar S, Jones R, Hilal MA, Andersson B, Boudjema K, Mullamitha S, Stassen L, Dasari BVM, Frampton AE, Aldrighetti L, Pellino G, Buchwald P, Gürses B, Wasserberg N, Gruenberger B, Spiers HVM, Jarnagin W, Vauthey JN, Kokudo N, Tejpar S, Valdivieso A, Adam R. Multisocietal European consensus on the terminology, diagnosis, and management of patients with synchronous colorectal cancer and liver metastases: an E-AHPBA consensus in partnership with ESSO, ESCP, ESGAR, and CIRSE. Br J Surg. 2023 Aug 11;110(9):1161-1170. doi: 10.1093/bjs/znad124. PMID: 37442562; PMCID: PMC10416695.
14. André T, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, Smith D, Garcia-Carbonero R, Benavides M, Gibbs P, de la Fouchardiere C, Rivera F, Elez E, Bendell J, Le DT, Yoshino T, Van Cutsem E, Yang P, Farooqui MZH, Marinello P, Diaz LA Jr; KEYNOTE-177 Investigators. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. N Engl J Med. 2020 Dec 3;383(23):2207-2218. doi: 10.1056/NEJMoa2017699. PMID: 33264544.
15. Lenz HJ, Van Cutsem E, Luisa Limon M, Wong KYM, Hendlisz A, Aglietta M, García-Alfonso P, Neyns B, Luppi G, Cardin DB, Dragovich T, Shah U, Abdullaev S, Gricar J, Ledeine JM, Overman MJ, Lonardi S. First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 Study. J Clin Oncol. 2022 Jan 10;40(2):161-170. doi: 10.1200/JCO.21.01015. Epub 2021 Oct 12. PMID: 34637336.
16. Sonbol MB, Siddiqi R, Uson PLS, Pathak S, Firwana B, Botrus G, Almader-Douglas D, Ahn DH, Borad MJ, Starr J, Jones J, Stucky CC, Smoot R, Riaz IB, Bekaii-Saab T. The Role of Systemic Therapy in Resectable Colorectal Liver Metastases: Systematic Review and Network Meta-Analysis. Oncologist. 2022 Dec 9;27(12):1034-1040. doi: 10.1093/oncolo/oyac212. PMID: 36239399; PMCID: PMC9732220.
17. Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, Crinò L, Benedetti G, Evangelista W, Fanchini L, Cortesi E, Picone V, Vitello S, Chiara S, Granetto C, Porcile G, Fioretto L, Orlandini C, Andreuccetti M, Masi G; Gruppo Oncologico Nord Ovest. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol. 2007 May 1;25(13):1670-6. doi: 10.1200/JCO.2006.09.0928. PMID: 17470860.
18. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfring GL, Miller LL. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med. 2000 Sep 28;343(13):905-14. doi: 10.1056/NEJM200009283431302. PMID: 11006366.
19. Ackerman NB. The blood supply of experimental liver metastases. IV. Changes in vascularity with increasing tumor growth. Surgery. 1974 Apr;75(4):589-96. PMID: 4840805.
20. Hendlisz A, Van den Eynde M, Peeters M, Maleux G, Lambert B, Vannoote J, De Keukeleire K, Verslype C, Defreyne L, Van Cutsem E, Delatte P, Delaunoit T, Personeni N, Paesmans M, Van Laethem JL, Flamen P. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol. 2010 Aug 10;28(23):3687-94. doi: 10.1200/JCO.2010.28.5643. Epub 2010 Jun 21. PMID: 20567019.
21. Lucchina N, Tsetis D, Ierardi AM, Giorlando F, Macchi E, Kehagias E, Duka E, Fontana F, Livraghi L, Carrafiello G. Current role of microwave ablation in the treatment of small hepatocellular carcinomas. Ann Gastroenterol. 2016 Oct-Dec;29(4):460-465. doi: 10.20524/aog.2016.0066. Epub 2016 Jun 24. PMID: 27708511; PMCID: PMC5049552.
22. Izzo F, Granata V, Grassi R, Fusco R, Palaia R, Delrio P, Carrafiello G, Azoulay D, Petrillo A, Curley SA. Radiofrequency Ablation and Microwave Ablation in Liver Tumors: An Update.

Oncologist. 2019 Oct;24(10):e990-e1005. doi: 10.1634/theoncologist.2018-0337. Epub 2019 Jun 19. PMID: 31217342; PMCID: PMC6795153.

23. Johnson LP, Rivkin SE. The implanted pump in metastatic colorectal cancer of the liver. Risk versus benefit. Am J Surg. 1985 May;149(5):595-8. doi: 10.1016/s0002-9610(85)80133-1. PMID: 3158217.
24. Standring O, Gholami S. Adjuvant hepatic artery infusion pump chemotherapy for resected colorectal cancer liver metastases. Surgery. 2023 Sep;174(3):747-749. doi: 10.1016/j.surg.2023.04.043. Epub 2023 Jun 14. PMID: 37321884.
25. Thiels CA, D'Angelica MI. Hepatic artery infusion pumps. J Surg Oncol. 2020 Jul;122(1):70-77. doi: 10.1002/jso.25913. Epub 2020 Mar 25. PMID: 32215927; PMCID: PMC9014308.
26. Pak LM, Kemeny NE, Capanu M, Chou JF, Boucher T, Cercek A, Balachandran VP, Kingham TP, Allen PJ, DeMatteo RP, Jarnagin WR, D'Angelica MI. Prospective phase II trial of combination hepatic artery infusion and systemic chemotherapy for unresectable colorectal liver metastases: Long term results and curative potential. J Surg Oncol. 2018 Mar;117(4):634-643. doi: 10.1002/jso.24898. Epub 2017 Nov 22. PMID: 29165816; PMCID: PMC5878699.
27. House MG, Kemeny NE, Gönen M, Fong Y, Allen PJ, Paty PB, DeMatteo RP, Blumgart LH, Jarnagin WR, D'Angelica MI. Comparison of adjuvant systemic chemotherapy with or without hepatic arterial infusional chemotherapy after hepatic resection for metastatic colorectal cancer. Ann Surg. 2011 Dec;254(6):851-6. doi: 10.1097/SLA.0b013e31822f4f88. PMID: 21975318.
28. Groot Koerkamp B, Sadot E, Kemeny NE, Gönen M, Leal JN, Allen PJ, Cercek A, DeMatteo RP, Kingham TP, Jarnagin WR, D'Angelica MI. Perioperative Hepatic Arterial Infusion Pump Chemotherapy Is Associated With Longer Survival After Resection of Colorectal Liver Metastases: A Propensity Score Analysis. J Clin Oncol. 2017 Jun 10;35(17):1938-1944. doi: 10.1200/JCO.2016.71.8346. Epub 2017 Apr 20. PMID: 28426374; PMCID: PMC5466010.
29. Kemeny NE, Niedzwiecki D, Hollis DR, Lenz HJ, Warren RS, Naughton MJ, Weeks JC, Sigurdson ER, Herndon JE 2nd, Zhang C, Mayer RJ. Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481). J Clin Oncol. 2006 Mar 20;24(9):1395-403. doi: 10.1200/JCO.2005.03.8166. Epub 2006 Feb 27. PMID: 16505413.
30. Allen-Mersh, T.G, S Earlam, C Fordy, K Abrams, J Houghton. Quality of life and survival with continuous hepatic-artery floxuridine infusion for colorectal liver metastases. The Lancet, Volume 344, Issue 8932, 1255 – 1260
31. van Hazel GA, Heinemann V, Sharma NK, Findlay MP, Ricke J, Peeters M, Perez D, Robinson BA, Strickland AH, Ferguson T, Rodríguez J, Kröning H, Wolf I, Ganju V, Walpole E, Boucher E, Tichler T, Shacham-Shmueli E, Powell A, Eliadis P, Isaacs R, Price D, Moeslein F, Taieb J, Bower G, Gebski V, Van Buskirk M, Cade DN, Thurston K, Gibbs P. SIRFLOX: Randomized Phase III Trial Comparing First-Line mFOLFOX6 (Plus or Minus Bevacizumab) Versus mFOLFOX6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients With Metastatic Colorectal Cancer. J Clin Oncol. 2016 May 20;34(15):1723-31. doi: 10.1200/JCO.2015.66.1181. Epub 2016 Feb 22. Erratum in: J Clin Oncol. 2016 Nov 20;34(33):4059. doi: 10.1200/JCO.2016.70.8982. PMID: 26903575.
32. Wasan HS, Gibbs P, Sharma NK, Taieb J, Heinemann V, Ricke J, Peeters M, Findlay M, Weaver A, Mills J, Wilson C, Adams R, Francis A, Moschandreas J, Virdee PS, Dutton P, Love S, Gebski V, Gray A; FOXFIRE trial investigators; SIRFLOX trial investigators; FOXFIRE-Global trial investigators; van Hazel G, Sharma RA. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncol. 2017 Sep;18(9):1159-1171. doi: 10.1016/S1470-2045(17)30457-6. Epub 2017 Aug 3. PMID: 28781171; PMCID: PMC5593813.
33. Uhlig J, Lukovic J, Dawson LA, Patel RA, Cavnar MJ, Kim HS. Locoregional Therapies for Colorectal Cancer Liver Metastases: Options Beyond Resection. Am Soc Clin Oncol Educ Book. 2021 Mar;41:133-146. doi: 10.1200/EDBK_320519. PMID: 34010047.
34. Ruers T, Van Coevorden F, Punt CJ, Pierie JE, Borel-Rinkes I, Ledermann JA, Poston G, Bechstein W, Lentz MA, Mauer M, Folprecht G, Van Cutsem E, Ducreux M, Nordlinger B; European Organisation for Research and Treatment of Cancer (EORTC); Gastro-Intestinal Tract Cancer Group; Arbeitsgruppe Lebermetastasen und tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO); National Cancer Research Institute Colorectal Clinical Study Group (NCRI CCSG). Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. J Natl Cancer Inst. 2017 Sep 1;109(9):djx015. doi: 10.1093/jnci/djx015. PMID: 28376151; PMCID: PMC5408999.
35. Wang J, Liang P, Yu J, Yu MA, Liu F, Cheng Z, Yu X. Clinical outcome of ultrasound-guided percutaneous microwave ablation on colorectal liver metastases. Oncol Lett. 2014 Jul;8(1):323-326. doi: 10.3892/ol.2014.2106. Epub 2014 Apr 29. PMID: 24959270; PMCID: PMC4063642.
36. Pathak S, Jones R, Tang JM, Parmar C, Fenwick S, Malik H, Poston G. Ablative therapies for colorectal liver metastases: a systematic review. Colorectal Dis. 2011 Sep;13(9):e252-65. doi: 10.1111/j.1463-1318.2011.02695.x. PMID: 21689362.
37. Shady W, Petre EN, Do KG, Gonen M, Yarmohammadi H, Brown KT, Kemeny NE, D'Angelica M, Kingham PT, Solomon SB, Sofocleous CT. Percutaneous Microwave versus Radiofrequency Ablation of Colorectal Liver Metastases: Ablation with Clear Margins (A0) Provides the Best Local Tumor Control. J Vasc Interv Radiol. 2018 Feb;29(2):268-275.e1. doi: 10.1016/j.jvir.2017.08.021. Epub 2017 Dec 6. PMID: 29203394; PMCID: PMC5803367.

Authors

Andrew B. Crocker, MD, St. Elizabeth Medical Center, Brighton, MA.

Munya H. Talukder, MD, St. Elizabeth Medical Center, Brighton, MA.

Mohammad S. Ali, MD, Boston University; Roger Williams Medical Center, Providence, RI.

Abdul Saied Calvino, MD, Boston University; Roger Williams Medical Center, Providence, RI.

Ponnandai Somasundar, MD, MPH, FACS, Boston University; Roger Williams Medical Center, Providence, RI.

N. Joseph Espat, MD, MS, FSSO, FACS, Boston University; Roger Williams Medical Center, Providence, RI.

Disclosures

None

Correspondence

N. Joseph Espat, MD

jespat@bu.edu

Current Applications of Intraperitoneal Chemotherapy

JENNA WILSON, DO; AISHWARYA AYYAPPAN, DO; ANDREW B. CROCKER, MD; STEVE KWON, MD

ABSTRACT

Peritoneal carcinomatosis presents significant therapeutic challenges due to the unique characteristics of peritoneal metastases, such as their widespread nature, variability in size, and limited blood supply. Intraperitoneal chemotherapy (IPC) was first introduced in 1955 as a targeted treatment modality to address these challenges. By delivering cytotoxic agents directly into the peritoneal cavity, IPC enhances drug concentration at tumor sites while minimizing systemic toxicity. Two primary methods of IPC are Hyperthermic Intraperitoneal Chemotherapy (HIPEC) and Early Postoperative Intraperitoneal Chemotherapy (EPIC), each with distinct protocols and advantages. HIPEC is administered during cytoreductive surgery under hyperthermic conditions, while EPIC is applied post-surgery over an extended period. Patient selection is critical, and the technique is most effective when tumor burden is manageable post-cytoreduction. This review explores the molecular properties of IPC agents, their clinical applications across various cancers, adverse effects, and long-term outcomes, highlighting IPC's potential as a life-saving treatment for patients with peritoneal metastases.

KEYWORDS: Intraperitoneal Chemotherapy; HIPEC; EPIC; peritoneal carcinomatosis

INTRODUCTION

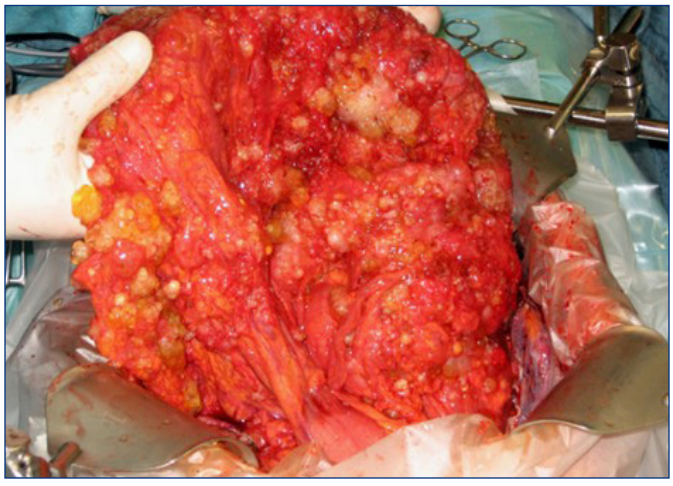
Peritoneal metastases pose a unique issue when considering treatment modalities. These tumors, often arising from colon, appendix, stomach and ovary, can be widespread, variable in size, and occupy organs with relatively sparse blood supply compared to other tumor locations.[1] Because of these characteristics, patients with peritoneal carcinomatosis are poor candidates for both local radiation therapy and systemic chemotherapy. This problem was first tackled in 1955 by Weissberger with the advent of intraperitoneal chemotherapy (IPC), an administration technique that allows for cytotoxic therapies to make direct contact with tumor deposits and penetrate via passive diffusion.[2] Since its introduction to the oncologic space, several patient populations with previously fatal prognoses have demonstrated significant benefit from its effects.[3] Our aim is to outline the specific current applications of IPC in terms of patient selection and cancer type, and to discuss adverse effects and overall clinical outcomes.

MECHANISM OF INTRAPERITONEAL CHEMOTHERAPY

IPC involves the direct instillation of cytotoxic drugs into the peritoneal cavity, maximizing drug-tumor cell contact.[2] The therapeutic agents reach tumor deposits through passive diffusion, allowing for enhanced local drug concentration while minimizing systemic toxicity.[2] This approach is particularly beneficial for treating peritoneal metastases, which are often difficult to reach through traditional systemic chemotherapy due to their limited vascular supply. IPC is more effective when the tumor deposits are small (typically no larger than 2.5 mm) as drug penetration is generally limited to 1–3 mm.[4] As such, cytoreductive surgery is crucial for reducing tumor burden prior to IPC[2] [**Figure 1**].

IPC agents are typically high molecular weight, hydrophilic, and ionized molecules. These properties facilitate the passive diffusion of the drugs into tumor deposits while limiting their passage across the plasma-peritoneal barrier, which helps reduce systemic toxicity.[6] Any drug that does cross the barrier is either metabolized by the liver or excreted by the kidneys, further minimizing bioavailability and preventing significant systemic effects.[1]

Figure 1. Omental caking due to peritoneal carcinomatosis – cytoreductive surgery[5]



HIPEC VS EPIC

The two primary IPC modalities are Hyperthermic Intraperitoneal Chemotherapy (HIPEC) and Early Postoperative Intraperitoneal Chemotherapy (EPIC). While the overarching goal of therapy are the same, they have important distinctions.

HIPEC is the intra-operative administration of cytotoxic drugs at an ideal temperature range of 41–43°C that allows for the synergistic destruction of tumor cells.[2] It is administered at the time of cytoreductive surgery for 30 to 120 minutes, just after resection has taken place and while the patient is still under general anesthesia. Hyperthermia is thought to amplify the cytotoxic effects of chemotherapy drugs through multiple mechanisms, particularly in hypoxic and nutrient-deprived environments.[10] By heating the chemotherapeutic agents to an ideal temperature of 41–43°C, the following changes occur:

1. The protein distribution across the plasma membranes of the tumor cells is shifted, leading to enhanced permeability of the tumor cells to the drugs;
2. The transmembrane efflux pumps are modulated to a lower functioning state;
3. DNA repair is impaired;
4. Heat shock proteins are activated.[10]

These changes enhance drug penetration and tumor cell destruction, and therefore, proponents of HIPEC believe hyperthermia to be an important component of HIPEC.

EPIC on the other hand, is administered on postoperative day one and can be readministered for up to seven days postoperatively. The cytotoxic drug is instilled and dwelled within the patient for 23 hours before draining and re-instilling the next day. Unlike HIPEC, EPIC utilizes cell cycle specific drugs which require prolonged tumor cell exposure and thus lengthened installation.[2]

The utilization of one modality over the other remains a matter of surgeon preference. Several studies have attempted to compare differences in survival outcomes and adverse effects when utilizing HIPEC vs EPIC. A recent study found EPIC to be an independent risk factor for major surgical complications.[7] Another study argued that HIPEC led to longer operative times, which naturally can lend itself to anesthesia-related complications.[7] Regardless of these findings, overall survival between the two groups were similar.[7] Certain retrospective analyses have also shown a benefit to overall survival when adding EPIC to CRS + HIPEC.[8] The addition of EPIC after initial treatment with CRS + HIPEC provides another opportunity to eradicate tumor cells that may have been left behind by HIPEC and incorporated themselves into postoperative adhesions. This has been named "the tumor entrapment theory," and poses a convincing argument to incorporate both modalities of IPC but can be challenging for patients to tolerate.[9]

PROCESS OF ADMINISTRATION

After complete cytoreduction surgery and before creation of any anastomoses, HIPEC can be administered by either the open abdomen or closed abdomen technique [**Figure 2**].

In the open abdomen technique, a Tenckhoff catheter is placed in the abdominal cavity as well as several closed suction drains.[1,2] The abdominal walls are suspended by a self-retractor and the open space is covered with a plastic sheet to maintain the elevated temperature. A heat exchanger is attached, and the chemotherapy is infused while the surgeon constantly manipulates and agitates the abdomen to ensure the solution covers as much surface area as possible. This is done for a duration of 30–120 minutes.[1,2]

The closed abdomen technique is similar, except that the skin edges are sutured after placement of the catheters in order to create a closed circuit for the perfusate to instill [**Figure 3**]. The volume of fluid is higher, as is the intra-abdominal pressure, which can aid in better tissue penetration. The closed technique also lessens heat dissemination due to the closed circuit.[1,2]

EPIC is administered on postoperative day one following cytoreduction surgery.[2] Intraperitoneal catheters are placed at the time of surgery, which are then used for the next one to seven days to percutaneously administer and then drain the cytotoxic medication once the 23-hour cycle completes.[2]

Figure 2. HIPEC machine (from ThermaSolutions)[11]

Figure 3. Intraoperative set up of HIPEC instillation – closed abdomen technique[12]

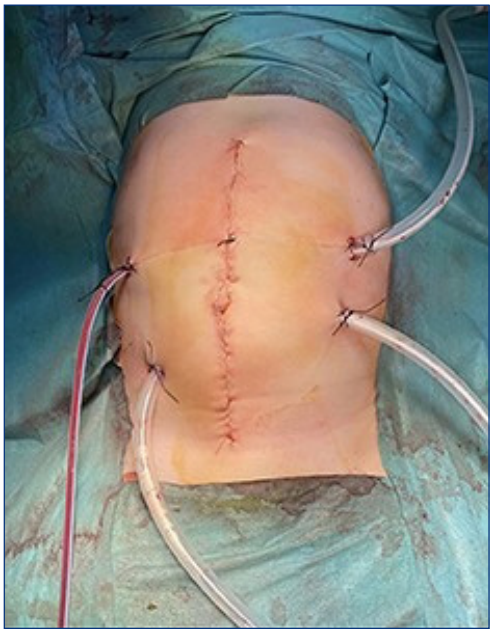
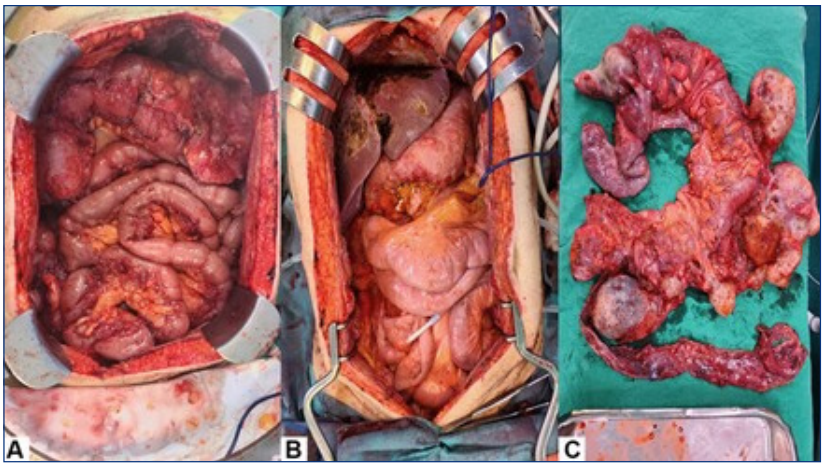


Figure 4. Before and after cytoreductive surgery with HIPEC30. [**A**] Before cytoreduction; [**B**] After cytoreductive surgery; [**C**] Tumor with involved organs removed



While EPIC provides the benefits of longer dwell times and repeated administration opportunities, it does have the limitations of potential patient discomfort as well as the lack of hyperthermic conditions.[2]

PATIENT SELECTION

Careful patient selection is crucial for the effective use of HIPEC. Treatment with HIPEC is generally reserved for patients with tumor burdens that can be feasibly removed on cytoreduction within 2-3 mm[13] [**Figure 4**]. Patients with larger or unresectable tumor burdens after cytoreduction are poor candidates due to limitations of chemotherapy penetration. Scoring systems such as the complete cytoreduction score are available to quantify residual tumor burden and have been shown to have prognostic significance for patient outcomes.[14] Similarly, patients must be able to tolerate cytoreduction and HIPEC administration. As a result, severe malnutrition and poor performance status are contraindications to this procedure just as with any other major surgery.[13] It is also recommended to delay or abort cytoreduction if there is concern for active peritonitis or sepsis.[13] Treatment agent specific contraindications are also important factors when considering patient selection for HIPEC, such as platinum-based chemotherapeutic agents, which are renally cleared and may not be tolerated by patients with renal disease.[13] An individualized and patient specific approach is important to optimize patient inclusion while limiting ineffective or potentially harmful attempts at treatment.

APPLICABLE CANCERS

Ovarian

The most common route of metastases of ovarian cancer to the peritoneum is by the shedding of cancerous ovarian cells into the peritoneal cavity.[15] The most common chemotherapeutic agent for ovarian cancer is cisplatin, administered every three weeks for six cycles.[2] Studies have demonstrated improved overall survival of patients with ovarian cancer when systemic chemotherapy was combined with IPC.[2] HIPEC and cytoreduction treatment was found to have a five-year progression free survival rate of 12.3% compared to 6.6% in patients who underwent surgery alone.[16]

Appendiceal/pseudomyxomaperitonei(PMP)

PMP is a difficult clinical condition in which a neoplasms, typically appendiceal in origin, secrete a gelatinous mucin causing profound mucinous ascites and can lead to bowel obstruction.[17] They have a characteristic peritoneal spread and have been shown to be responsive to CRS + HIPEC. The most commonly used agent for PMP is mitomycin C, typically administered in two separate doses[2]. Treatment with cytoreduction and HIPEC was found to be associated with 10-year overall survival rates of 37% versus 16% in patients who underwent surgery alone.[18]

Gastric

Carcinomatosis due to gastric cancer represents a majority of gastric cancer related deaths at a range of 53–60%.[19] The use of both HIPEC and EPIC in peritoneal gastric cancer has been studied and shown to be effective for improving survival. HIPEC typically uses mitomycin C and cisplatin, while EPIC uses 5-FU.[2] In patients who underwent surgery alone versus HIPEC and surgery, overall five-year survival rates improved from 53.4 to 86.8%.[20]

Colorectal

Colorectal cancer continues to occupy a large portion of annual cancer deaths, ranking at number two in the US in terms of cancer-related mortality. Researchers have estimated up to 10% of patients have peritoneal spread at the time of diagnosis, making this a significant patient population to be considered for IPC.[21] While systemic therapy with FOLFOX and certain biologics remain a mainstay of colorectal cancer treatment, when HIPEC is employed for peritoneal metastases, mitomycin C as well as oxaliplatin are often used.[2] Compared to systemic chemotherapy alone, there was improved outcomes in survival in those who received combined cytoreductive surgery and HIPEC where median survival lengthened from three to seven months to 41 months.[22]

Malignant peritoneal mesothelioma

Typically related to asbestos exposure, malignant peritoneal mesothelioma is a rare, aggressive entity that leads to the formation of plaque-like tumor deposits within the abdominal

cavity.[23] Prior to the development of IPC, the median survival with systemic chemotherapy, surgical resection, and total abdominal radiation was 12 months.[23] Now, CRS + HIPEC ± EPIC is used for MPM and has increased the median survival up to 92 months.[23] The most common agents used in HIPEC for MPM are mitomycin C, doxorubin, and cisplatin, while paclitaxel is commonly used in EPIC.[2]

AGENTS

As previously discussed, the ideal IPC drug is one that has a high molecular weight, hydrophilicity, and is ionized. These properties allow for maximal penetration into micrometastases while reducing systemic toxicity.[2] Currently, the most commonly used agent in US is Mitomycin C(MMC).[24] It works by adding alkyl groups to DNA, leading to cross-linking and strand breaks, which hinders cancer cell replication.[25] MMC is often used in HIPEC due to its favorable pharmacokinetics, including a satisfactory area under the curve (AUC) ratio of intraperitoneal to plasma concentrations, high tissue penetration distance of up to 5mm, low systemic absorption rate, stability at elevated temperatures, and synergistic effects with heat. It is the drug of choice for appendiceal, colorectal, and, in combination with other drugs, gastric malignancies.[2] Other agents that have shown to be effective with tolerable side effect profiles include 5-FU, oxaliplatin, doxorubicin, cisplatin, and paclitaxel.[2]

COMPLICATIONS/ADVERSE EFFECTS

The combined treatment of cytoreductive surgery and HIPEC has been associated with mortality rates of 0–18% and morbidity rate between 30–70%.[26] The PRODIGE 7 trial comparing cytoreductive surgery and HIPEC vs. cytoreductive surgery alone demonstrated an increased rate of 26% versus 15% occurrence of grade 3 or worse events within 60 days of treatment.[27] Common postoperative complications include enterocutaneous fistulas, neutropenia, post-operative bleeding, anastomotic leaks, systemic sepsis, and infection.[28] Of the various post-operative complications, the most common is infections, resulting in a decreased overall survival and recurrence free survival rate.[28] After initial surgery, there was an associated re-operation rate of 14.5% performed seven to nine days after initial treatment for fascial dehiscence, intraabdominal hemorrhage and anastomotic leak along with a 1–4% 30-day mortality rate.[26,29] Factors associated with increased morbidity and mortality are increased age, hypoalbuminemia, high peritoneal carcinomatosis index, cytoreductive surgery involving bowel resection, diaphragmatic involvement, performance of distal pancreatectomy, hepatobiliary and urologic procedures.[26]

OUTCOMES

The beneficial outcomes of IPC in patients with peritoneal metastases and malignancies range from increased long-term survival to improved quality of life. While these metrics vary depending on the type of cancer and individual patient, several studies have correlated IP with better outcomes.

A retrospective study in 2015 looking at 876 patients with metastatic ovarian cancer demonstrated a median survival of 61.8 months (95% CI, 55.5 to 69.5) in the IP chemotherapy group compared to 51.4 months (95% CI, 46.0 to 58.2) in the intravenous systemic chemotherapy group.[31] They also showed that for each cycle of IP chemotherapy completed, the risk of death decreased by 12% (AHR, 0.88; 95% CI, 0.83 to 0.94; P < .001).[31] After a median follow-up of over 10 years, the HIPEC group exhibited a median overall survival of 44.9 months, compared to 33.3 months in the surgery-only group.[32] The five-year overall survival rates were 36.9% for the HIPEC group versus 19.7% for the control group, and the 10-year overall survival rates were 16.1% versus 10.9%, respectively.[32] Multiple other studies have concluded that there was an improved overall survival when IPC is administered.[1]

Beyond survival, peritoneal carcinomatosis can also be extremely life-limiting due to its associated symptoms. McQuellen et al used various scales to assess the quality of life (QoL) and functional status of patients after treatment with IPC.[33] Using the Functional Assessment of Cancer Therapy–Colon (FACT-C) scale, a measure of QoL after debulking and HIPEC, they found that the majority of patients returned to their functional baseline by three months post-treatment.[33] Dodson et al used several scales of measure, including the SF-36 Physical Functioning scale, FACT-C, the Brief Pain Inventory, the Center for Epidemiologic Studies Depression scale, and the Eastern Cooperative Oncology Group (ECOG) performance status, and concluded that the majority of patients showed an improved scoring at six months after treatment with CRS and HIPEC.[34] Even for patients seeking palliation only, the administration of IPC can contribute to improved quality of life by lessening pain, decreasing bloating and early satiety, and lessening the need for paracentesis in cases of advanced pseudomyxoma peritonei.[35]

FUTURE DIRECTIONS

IPC is a consistently evolving treatment option for the management of peritoneal malignancies. One promising avenue of development is the use of neoadjuvant intraperitoneal and systemic chemotherapy (NIPS).[36] This approach has been shown to be a feasible option to reduce tumor burden and improve the likelihood of resection with negative margins.[36] Prospective research regarding efficacy and ideal patient selection for NIPS is ongoing.[37] As laparoscopic and robotic surgery continues to push the boundaries of what can be

accomplished without open surgery, minimally invasive CRS and HIPEC may also become more frequently utilized.[38] With more data from ongoing studies becoming available, standardized protocols should be established as few are currently available.[1] IPC remains an area of active research and development with exciting potential to improve patient outcomes moving forward.

CONCLUSION

IPC allows for localized high-dose drug delivery directly to the peritoneal cavity, overcoming limitations of other treatment modalities. While HIPEC and EPIC are the primary IPC techniques, current evidence does not show a clear advantage of one over the other. IPC has demonstrated survival benefits in select malignancies, particularly ovarian and colorectal cancers, but results in gastric cancer and other peritoneal surface malignancies remain investigational. Further research is needed to optimize patient selection, refine treatment protocols, and clarify IPC's long-term benefits in managing peritoneal metastases.

References

1. Ben Aziz M, Di Napoli R. Cytoreduction (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC). In: *StatPearls*. StatPearls Publishing; 2025. Accessed March 17, 2025. http://www.ncbi.nlm.nih.gov/books/NBK570563/
2. Goodman MD, McPartland S, Detelich D, Saif MW. Chemotherapy for intraperitoneal use: a review of hyperthermic intraperitoneal chemotherapy and early post-operative intraperitoneal chemotherapy. *J Gastrointest Oncol*. 2016;7(1):45-57. doi:10.3978/j.issn.2078-6891.2015.111
3. Foster JM, Sleightholm R, Patel A, et al. Morbidity and Mortality Rates Following Cytoreductive Surgery Combined With Hyperthermic Intraperitoneal Chemotherapy Compared With Other High-Risk Surgical Oncology Procedures. *JAMA Netw Open*. 2019;2(1):e186847. doi:10.1001/jamanetworkopen.2018.6847
4. Rationale and techniques of intra-operative hyperthermic intraperitoneal chemotherapy - PubMed. Accessed March 17, 2025. https://pubmed.ncbi.nlm.nih.gov/11908929/
5. Glockzin G, Schlitt HJ, Piso P. Peritoneal carcinomatosis: patients selection, perioperative complications and quality of life related to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *World J Surg Oncol*. 2009;7:5. doi:10.1186/1477-7819-7-5
6. Yan TD, Cao CQ, Munkholm-Larsen S. A pharmacological review on intraperitoneal chemotherapy for peritoneal malignancy. *World J Gastrointest Oncol*. 2010;2(2):109-116. doi:10.4251/wjgo.v2.i2.109
7. Jeong MH, Kang SJ, Park SY, et al. Comparison of EPIC Versus HIPEC in the Treatment of Colorectal Peritoneal Metastases and Appendix Tumors Using Inverse Probability of Treatment Weighting. *Ann Surg Oncol*. 2024;31(10):7111-7121. doi:10.1245/s10434-024-15674-2
8. Soucisse ML, Liauw W, Hicks G, Morris DL. Early postoperative intraperitoneal chemotherapy for lower gastrointestinal neoplasms with peritoneal metastasis: a systematic review and critical analysis. *Pleura Peritoneum*. 2019;4(3):20190007. doi:10.1515/pp-2019-0007
9. Sugarbaker PH. A narrative review of what can HIPEC do. *Eur J Surg Oncol*. 2023;49(9):106976. doi:10.1016/j.ejso.2023.07.002
10. Helderman RFCPA, Löke DR, Kok HP, et al. Variation in Clinical Application of Hyperthermic Intraperitoneal Chemotherapy: A Review. *Cancers*. 2019;11(1):78. doi:10.3390/cancers11010078
11. ThermaSolutions – Hyperthermic Intraperitoneal Chemotherapy. ThermaSolutions – Hyperthermic Intraperitoneal Chemotherapy. Accessed March 19, 2025. https://www.thermasolutions.com/
12. Garnier H, Murawski M, Jastrzebski T, et al. Case Report: Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy Application in Intraperitoneally Disseminated Inflammatory Myofibroblastic Tumor and in the Youngest Patient in the World: New Indication and Modification of Technique. *Front Surg*. 2021;8:746700. doi:10.3389/fsurg.2021.746700
13. Simkens GA, Rovers KP, Nienhuijs SW, de Hingh IH. Patient selection for cytoreductive surgery and HIPEC for the treatment of peritoneal metastases from colorectal cancer. *Cancer Manag Res*. 2017;9:259-266. doi:10.2147/CMAR.S119569
14. Munoz-Zuluaga CA, King MC, Diaz-Sarmiento VS, et al. Defining "Complete Cytoreduction" After Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (CRS/HIPEC) for the Histopathologic Spectrum of Appendiceal Carcinomatosis. *Ann Surg Oncol*. 2020;27(13):5026-5036. doi:10.1245/s10434-020-08844-5
15. Yeung TL, Leung CS, Yip KP, Au Yeung CL, Wong STC, Mok SC. Cellular and molecular processes in ovarian cancer metastasis. A Review in the Theme: Cell and Molecular Processes in Cancer Metastasis. *Am J Physiol - Cell Physiol*. 2015;309(7):C444-C456. doi:10.1152/ajpcell.00188.2015
16. HIPEC/Cytoreduction Produces Long-Term Survival in Advanced Ovarian Cancer. Cancer Network. December 19, 2023. Accessed March 17, 2025. https://www.cancernetwork.com/view/hipec-cytoreduction-produces-long-term-survival-in-advanced-ovarian-cancer
17. Scally CP, Fournier KF, Mansfield PF. Hyperthermic Intraperitoneal Chemotherapy in Pseudomyxoma Peritonei After Cytoreductive Surgery. *JAMA Surg*. 2021;156(3):e206364. doi:10.1001/jamasurg.2020.6364
18. Wang B, Ma R, Shi G, Fan X, Rao B, Xu H. Hyperthermic intraperitoneal chemotherapy in patients with incomplete cytoreduction for appendiceal pseudomyxoma peritonei: a 10-year treatment experience in China. *Orphanet J Rare Dis*. 2024;19(1):8. doi:10.1186/s13023-023-02995-w
19. Okines A, Verheij M, Allum W, Cunningham D, Cervantes A. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2010;21:v50-v54. doi:10.1093/annonc/mdq164
20. Wu Z, Li Z, Ji J. Morbidity and mortality of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in advanced gastric cancer. *Transl Gastroenterol Hepatol*. 2016;1:63. doi:10.21037/tgh.2016.07.03
21. Drittone D, Schipilliti FM, Arrivi G, Mazzuca F. Cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy applications in upper and lower gastrointestinal cancer, a review. *Oncol Rev*. 2024;18:1496141. doi:10.3389/or.2024.1496141
22. Sarofim M, Wijayawardana R, Ahmadi N, Morris DL. Repeat cytoreductive surgery with HIPEC for colorectal peritoneal metastases: a systematic review. *World J Surg Oncol*. 2024;22(1):99. doi:10.1186/s12957-024-03386-6
23. Enomoto LM, Shen P, Levine EA, Votanopoulos KI. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal mesothelioma: patient selection and special considerations. *Cancer Manag Res*. 2019;11:4231-4241. doi:10.2147/CMAR.S170300
24. Ihemelandu CU, Shen P, Stewart JH, Votanopoulos K, Levine EA. Management of Peritoneal Carcinomatosis from Colorectal Cancer. *Semin Oncol*. 2011;38(4):568-575. doi:10.1053/j.seminoncol.2011.05.011

25. Mitomycin C. An overview | ScienceDirect Topics. Accessed March 19, 2025. https://www.sciencedirect.com/topics/chemistry/mitomycin-c
26. Newton AD, Bartlett EK, Karakousis GC. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a review of factors contributing to morbidity and mortality. *J Gastrointest Oncol*. 2016;7(1). doi:10.3978/j.issn.2078-6891.2015.100
27. Quénet F, Elias D, Roca L, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(2):256-266. doi:10.1016/S1470-2045(20)30599-4
28. Gamboa AC, Lee RM, Turgeon MK, et al. Implications of Postoperative Complications for Survival After Cytoreductive Surgery and HIPEC: A Multi-Institutional Analysis of the US HIPEC Collaborative. *Ann Surg Oncol*. 2020;27(13):4980-4995. doi:10.1245/s10434-020-08843-6
29. Blaj S, Nedelcut S, Mayr M, et al. Re-operations for early postoperative complications after CRS and HIPEC: indication, timing, procedure, and outcome. *Langenbecks Arch Surg*. 2019;404(5):541-546. doi:10.1007/s00423-019-01808-8
30. Cytoreductive surgery and intraperitoneal chemotherapy for peritoneal metastasis of colorectal cancer: long-term follow-up results at a single institution in Korea | Request PDF. *ResearchGate*. Published online October 22, 2024. doi:10.1007/s00384-023-04340-w
31. Tewari D, Java JJ, Salani R, et al. Long-term survival advantage and prognostic factors associated with intraperitoneal chemotherapy treatment in advanced ovarian cancer: a gynecologic oncology group study. *J Clin Oncol Off J Am Soc Clin Oncol*. 2015;33(13):1460-1466. doi:10.1200/JCO.2014.55.9898
32. Aronson SL, Lopez-Yurda M, Koole SN, et al. Cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy in patients with advanced ovarian cancer (OVHIPEC-1): final survival analysis of a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2023;24(10):1109-1118. doi:10.1016/S1470-2045(23)00396-0
33. McQuellon RP, Loggie BW, Fleming RA, Russell GB, Lehman AB, Rambo TD. Quality of life after intraperitoneal hyperthermic chemotherapy (IPHC) for peritoneal carcinomatosis. *Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol*. 2001;27(1):65-73. doi:10.1053/ejso.2000.1033
34. Dodson RM, McQuellon RP, Mogal HD, et al. Quality-of-Life Evaluation After Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy. *Ann Surg Oncol*. 2016;23(Suppl 5):772-783. doi:10.1245/s10434-016-5547-y
35. Lambert LA, Harris A. Palliative cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion: current clinical practice or misnomer? *J Gastrointest Oncol*. 2016;7(1):112-121. doi:10.3978/j.issn.2078-6891.2015.132
36. Fujiwara Y, Takiguchi S, Nakajima K, et al. Neoadjuvant intraperitoneal and systemic chemotherapy for gastric cancer patients with peritoneal dissemination. *Ann Surg Oncol*. 2011;18(13):3726-3731. doi:10.1245/s10434-011-1770-8
37. Lu S, Yang ZY, Yan C, et al. A Phase III Trial of Neoadjuvant Intraperitoneal and Systemic Chemotherapy for Gastric Cancer with Peritoneal Metastasis. *Future Oncol*. 2022;18(10):1175-1183. doi:10.2217/fon-2021-1414
38. Ortega J, Orfanelli T, Levine E, Konstantinidis IT. The robotic future of minimally invasive cytoreduction and hyperthermic intraperitoneal chemotherapy for peritoneal surface malignancies. *Chin Clin Oncol*. 2023;12(2):16-16. doi:10.21037/cco-22-118

Authors

Jenna Wilson, DO, St. Elizabeth Medical Center, Brighton, MA.

Aishwarya Ayyappan, DO, St. Elizabeth Medical Center, Brighton, MA.

Andrew B. Crocker, MD, St. Elizabeth Medical Center, Brighton, MA.

Steve Kwon, MD, Boston University; Roger Williams Medical Center, Providence, RI.

Disclosures

None

Correspondence

steve.kwon@chartercare.org

Minimally Invasive Liver Surgery for Primary and Secondary Liver Malignancies

MUNYA H. TALUKDER, MD; JENNA WILSON, DO; ANDREW B. CROCKER, MD; ALI AHMAD, MD, FACS; PONNANDAI SOMASUNDAR, MD, MPH, FACS

ABSTRACT

Minimally invasive (MIS) liver surgery has grown tremendously in the past two decades and today represents a major weapon in the fight against primary and metastatic neoplasms of the liver. This review catered towards the modern evolution of MIS hepatectomy techniques in addition to the role of robotic surgery in this field. The article also addresses the utility of advanced intra-operative techniques in hepatic parenchymal transection ranging from the Glissonian pedicle approach to the use of indocyanine green (ICG) guided near-infrared fluorescence in non-anatomic resections. In addition, we briefly discuss ablation techniques utilized for liver cancer, including microwave ablation and the novel histotripsy ablation.

KEYWORDS: Minimally invasive; laparoscopic; robotic; hepatectomy; ablation

INTRODUCTION

In current times, surgical resection is still considered the gold standard treatment for patients with resectable liver malignancies. Liver surgery has dramatically evolved in recent decades, improving its safety profile with peri-operative mortality rates below 2% for most MIS hepatectomies.[1] Successful oncologic outcomes in liver surgery are reliant on obtaining a R0 resection margin with preservation of healthy liver parenchyma.

Surgery remains the mainstay of treatment in patients with primary hepatic neoplasms such as hepatocellular carcinoma (HCC) and intra-hepatic cholangiocarcinoma (ICC).[2] The use of MIS approach to hepatectomy for HCC has shown promise worldwide, with up to 30% of HCC resections estimated to be minimally invasive.[3] The majority of patients with HCC also harbor chronic liver disease (CLD). The presence of CLD and liver cirrhosis pose substantial challenges such as increased hemorrhagic complications and higher rates of post-hepatectomy liver failure (PHLF). Therefore, locoregional tumor ablative treatments such as microwave ablation (MWA), trans-arterial chemoembolization (TACE) and Yttrium-90 (Y-90) radio-embolization have gained substantial traction. In addition, liver transplant remains a viable option for some patients with HCC who meet the criteria.

Colorectal cancer liver metastasis (CRLM) is the most common indication for MIS hepatectomy in the United States; about a quarter of laparoscopic liver resection (LLR) for malignancy is performed for CRLM.[4] Liver resection (LR) for CRLM in selected patients offers excellent oncologic outcomes, with a five-year overall survival rate of 40–50%.[5]

In the modern era, robotic surgery has allowed for expansion of MIS approach to liver surgery. The technological advantages offered by the robotic platform, such as multi-articulated instruments, increased dexterity along with the 3D visualization, has allowed surgeons to tackle more complex resections via MIS approach.

Parenchymal transection techniques have also evolved with a drive towards parenchyma preservation. The past decade has seen a substantial increase in non-anatomic parenchyma-sparing resections with an expected decrease in the rate of extended hepatectomies. Owing to this paradigm shift in the surgical management of liver metastases, techniques such as ICG-guided resections and Glissonian pedicle guided segmentectomies have emerged as attractive approaches to tackle non-anatomic and anatomic resections.

LAPAROSCOPIC LIVER RESECTION

Similar to minimally invasive surgery in other fields, LLR for hepatic pathology has been increasingly utilized over the last several decades with promising results in the literature. Two international consensus conferences and several retrospective studies supported that LLR is equivalent to open approach for both minor and major hepatic resections in terms of oncological outcomes, but is associated with less blood loss, decreased postoperative morbidity and a shorter hospital stay.[6] A randomized control study, conducted to evaluate Enhanced recovery after surgery (ERAS) in LLR verified these advantages. For example, the median postoperative hospital stay was 6.2 (±2.6) days in the ERAS group, compared to 9.9 (±5.9) days in the control group (p-value<0.01). The morbidity rate was 22.5% (18 of 80 patients) in the ERAS group and 43.9% (47 of 107 patients) in the control group (P = 0.002).[7] While MIS approach has been shown to be safe and effective relative to open surgery, surgeon comfort remains an important factor in the use of LLR.

ROBOTIC HEPATECTOMY

Robotic surgery has the potential to overcome some of the limitations of laparoscopy. The stability of the robotic platform, combined with the 3D, magnified high-definition vision, increased degrees of freedom of the instruments and tremor filtering provide higher dexterity to the surgeon and allow for the same movements of open surgery. Furthermore, the robotic platform allows for easier integration of technologies, such as near-infrared fluorescence for vascular and biliary identification and 3D ultrasound instruments with integrated probes for section margin assessment. In 2014, Tsung et al performed a matched series comparison of surgical and postsurgical outcomes between robotic (n=57), laparoscopic (n=114), and open hepatic resections (n=21). A statistically significant difference was seen when comparing the EBL of robotic versus open surgery, as well as in the hospital length of stay.[8] With continued technological advances and improved access to robotic consoles, the role of robotic hepatectomies should continue to develop over time.

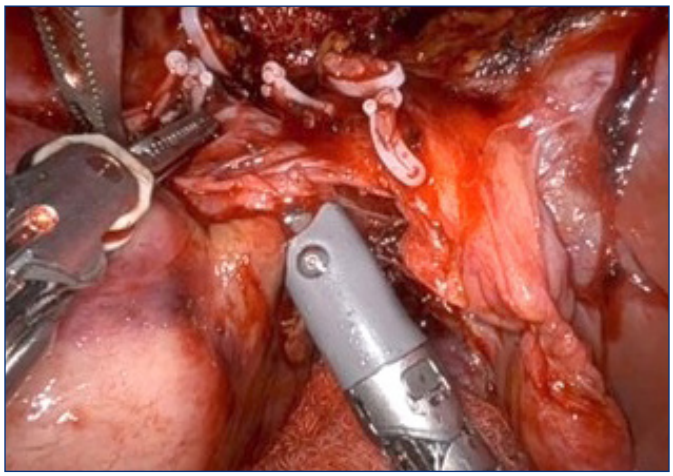
GLISSONIAN PEDICLED APPROACHES

In recent years, parenchymal-sparing liver resections have become the cornerstone approach to preserve residual liver volume, decrease postoperative liver failure, and enhance the possibility of repeated liver resection rates.[9] Small anatomical resections using ICG and Glissonian approaches are techniques employed to achieve a successful parenchymal-sparing liver resection.

The Glisson's capsule wraps the hepatic artery, the portal vein and the bile duct in the liver and forms bundles at the hepatic hilus and in the liver as the Glissonian pedicle tree **(Figure 1)**. The capsule does not connect to the proper membrane of the liver. Therefore, the Glissonian pedicles can be detached from the liver parenchyma without liver dissection. When the Glissonian pedicles are ligated before liver transection, various types of anatomical hepatectomy can be carried out.[10]

Intraoperative bleeding is a predictor of postoperative outcomes following liver surgery; therefore, it is crucial to have vascular control during liver resection. In addition, preservation of future liver remnant is critical in preventing post-hepatectomy liver failure as one of the main causes of postoperative morbidity and mortality. The Glissonian approach to liver resection offers an effective method for vascular inflow control while protecting future liver remnant from ischemia-reperfusion injury. With increasing popularity of minimally invasive surgery, laparoscopic liver resection via Glissonian approach has been shown to be superior to standard laparoscopic hepatectomy.[11] In the intrahepatic Glissonian approach small incisions on well-defined anatomical landmarks are performed to approach the pedicles of both right and left liver, making dissection of the hilar plate unnecessary. Intrahepatic access to Glissonian

Figure 1. Glissonian Pedicle



pedicles complements laparoscopy, since it avoids unnecessary extensive dissection along the hepatic hilum during laparoscopic procedures, which are technically complex and potentially time-consuming with high morbidity. [12]

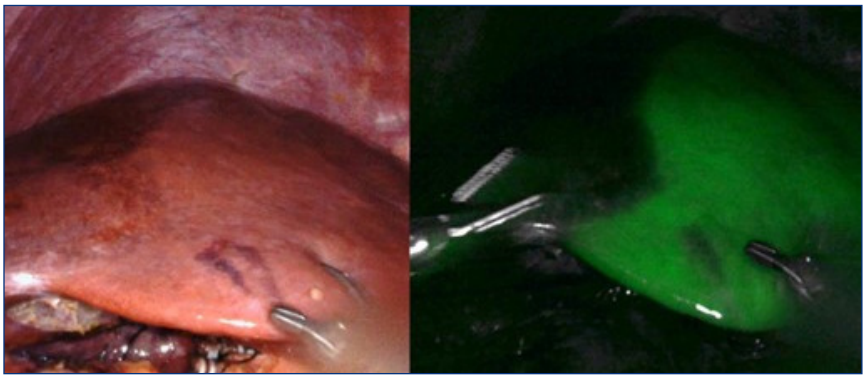
MINIMALLY INVASIVE MAJOR HEPATECTOMY

Major hepatectomy is a complex procedure that requires advanced surgical knowledge and skills. Although minimally invasive resections of the liver have been performed more frequently in recent years, major resections are still a minority of those cases. Current data on these numbers is somewhat sparse, but one report described that out of 149 robotic liver cases studied, 47% of them counted as major resections.[13] The largest series of robotic hepatectomy was reported by Giulianotti et al in 2011 with a total of 70 hepatic resections, of which 27 were major hepatectomies.[14] Spampinato et al performed a retrospective study comparing the perioperative outcomes of robot-assisted major hepatectomy and laparoscopic major hepatectomy in four Italian centers. A total of 50 major hepatectomies were considered, including 25 robotic and 25 laparoscopic resections. The mean robotic operative time was 430 minutes with a median EBL of 250 mL, comparable to laparoscopy.[15]

INDOCYANINE GREEN (ICG) AND INTRA-OPERATIVE ULTRASOUND (IOUS)

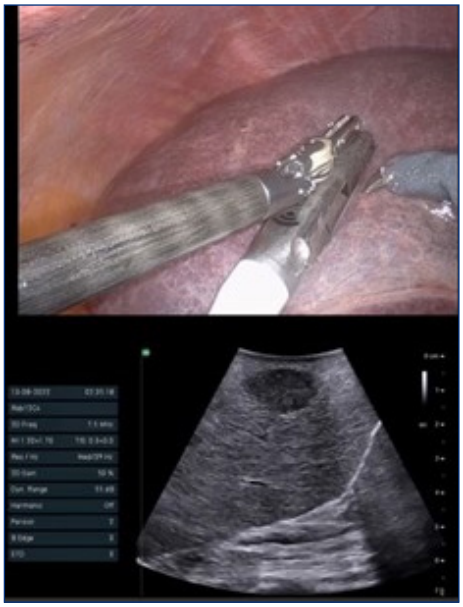
Due to the intricate anatomy and 3D contouring of the liver segments, non-anatomic parenchymal sparing resections can be technically challenging. Use of adjuncts such as intra-operative ultrasound (IOUS) and ICG fluorescence can help with adequate mapping of tumors in relation to vasculo-biliary pedicles. The use of intraoperative ICG fluorescence has been proven to be a high potential navigation tool during liver surgery. The variability of ICG accumulation within tumors as opposed to the background hepatic parenchyma

Figure 2. Indocyanine Green (ICG)



allows for precise anatomic delineation of lesions for safe liver resection [**Figure 2**]. Studies have reported higher detection rates of primary lesions and additional metastases after intravenous administration of ICG.[16] Handgraaf et al reported better survival after ICG-oriented liver resections due to the resection of additional nodules, which had been missed by conventional imaging.[17] Marino et al compared robot-assisted liver resections with and without additional ICG application and reported significantly higher R0 resection rates after ICG application.[18] However, since the plasma clearance of ICG is primarily dependent on hepatocyte function, the sensitivity of ICG-guided tumor detection is somewhat limited in patients suffering from advanced liver cirrhosis. Although early data is promising, further studies are needed to determine the true benefit and potential pitfalls of ICG guided hepatectomies including its use among patients with cirrhosis.

Figure 3. Intra-operative Ultrasound



Intra-operative liver ultrasound can also provide an additionally useful adjunct in mapping of tumors in relation to inflow pedicles and outflow veins. Assessment of such anatomy can prove critical in surgical planning especially in the context of non-anatomic resections. With the newer robotic platforms, IOUS can be used with a flexible cord allowing it to be used with high accuracy even in difficult to visualize portions such as the posterior and superior segments of the liver. **Figure 3** shows an intra-operative picture of IOUS being used during a hepatectomy procedure.

MICROWAVE/THERMAL ABLATION

Resection is the standard of care for patients with resectable primary and secondary liver cancers. However, large number of patients who are diagnosed with primary and secondary liver cancers are not eligible for resection or transplantation due to inadequate functional liver function, and multifocal or advanced disease. As a result, microwave (MVA) and radiofrequency thermal ablations (RFA) are increasingly utilized. Both RFA/MWA induce tumor cell death through frictional heating resulting in protein denaturation and coagulation necrosis. MWA generates heat at a faster rate, creates larger ablation zones, and have reduced heat-sink effect compared to RFA leading to more utilization when tumors are nearby vascular structures.[19]

HISTOTRIPSY ABLATION

Histotripsy is a novel non-invasive technique recently FDA-approved to treat liver cancers. It utilizes focused ultrasound to ablate targeted regions of tissues into acellular debris. The first human clinical trial of histotripsy for liver cancers, named the THERESA Study (NCT03741088), resulted in the establishment of histotripsy's efficacy in destroying targeted tissue without harmful device-related effects.[20] Studies further suggests that local tumor ablation by histotripsy induces systemic immunomodulation, contributing to enhanced anti-tumor responses that can synergistically work with immunotherapy. Considering that this combinatorial approach with histotripsy potentially leads to better prognosis for cancer patients, it will be pivotal to translate these findings into clinical use to effectively optimize the potency of immunotherapy.[21]

CONCLUSION

Liver resection continues to be the gold standard treatment for patients with liver malignancies. such as hepatocellular carcinoma (primary liver cancers) and colorectal liver metastasis (secondary liver cancers). Minimally invasive liver surgery is increasingly used over open approach with data showing reduced postoperative morbidity/complications and length of stay. Current technological advances such as robotic platform have facilitated this trend by making liver MIS safer and more precise. By understanding available treatment options and cultivating a patient centered approach to treatment planning, we can continue to improve the treatment of patients with primary and secondary liver malignancies.

References

1. Ban D, Tanabe M, Kumamaru H, Nitta H, Otsuka Y, Miyata H, Kakeji Y, Kitagawa Y, Kaneko H, Wakabayashi G, Yamaue H, Yamamoto M. Safe Dissemination of Laparoscopic Liver Resection in 27,146 Cases Between 2011 and 2017 From the National Clinical Database of Japan. Ann Surg. 2021 Dec 1;274(6):1043-1050. doi: 10.1097/SLA.0000000000003799. PMID: 32209896.
2. Morise Z. Current status of minimally invasive liver surgery for cancers. World J Gastroenterol. 2022 Nov 21;28(43):6090-6098. doi: 10.3748/wjg.v28.i43.6090. PMID: 36483154; PMCID: PMC9724486.
3. Xourafas D, Pawlik TM, Cloyd JM. Early Morbidity and Mortality after Minimally Invasive Liver Resection for Hepatocellular Carcinoma: a Propensity-Score Matched Comparison with Open Resection. J Gastrointest Surg. 2019 Jul;23(7):1435-1442. doi: 10.1007/s11605-018-4016-2. Epub 2018 Oct 30. PMID: 30377911.
4. Cherqui D. Evolution of laparoscopic liver resection. Br J Surg. 2016 Oct;103(11):1405-7. doi: 10.1002/bjs.10252. Epub 2016 Jul 27. PMID: 27464356.
5. Newhook TE, Vauthey JN. Colorectal liver metastases: state-of-the-art management and surgical approaches. Langenbecks Arch Surg. 2022;407:1765–1778. doi: 10.1007/s00423-022-02496-7.
6. Jia C, Li H, Wen N, Chen J, Wei Y, Li B. Laparoscopic liver resection: a review of current indications and surgical techniques. Hepatobiliary Surg Nutr. 2018 Aug;7(4):277-288. doi: 10.21037/hbsn.2018.03.01. PMID: 30221155; PMCID: PMC6131258.
7. Liang X, Ying H, Wang H, Xu H, Yu H, Cai L, Wang Y, Tong Y, Ji L, Luo R, Cai XJ. Enhanced Recovery Program Versus Traditional Care in Laparoscopic Hepatectomy. Medicine (Baltimore). 2016 Feb;95(8):e2835. doi: 10.1097/MD.0000000000002835. PMID: 26937913; PMCID: PMC4779010.
8. Giulianotti PC, Bianco FM, Daskalaki D, Gonzalez-Ciccarelli LF, Kim J, Benedetti E. Robotic liver surgery: technical aspects and review of the literature. Hepatobiliary Surg Nutr. 2016 Aug;5(4):311-21. doi: 10.21037/hbsn.2015.10.05. PMID: 27500143; PMCID: PMC4960413.
9. Okumura S, Tabchouri N, Leung U, Tinguely P, Louvet C, Beaussier M, Gayet B, Fuks D. Laparoscopic parenchymal-sparing hepatectomy for multiple colorectal liver metastases improves outcomes and salvageability: A propensity score-matched analysis. Ann. Surg. Oncol. 2019;26:4576–4586. doi: 10.1245/s10434-019-07902-x.
10. Yamamoto M, Ariizumi SI. Glissonean pedicle approach in liver surgery. Ann Gastroenterol Surg. 2018 Feb 13;2(2):124-128. doi: 10.1002/ags3.12062. PMID: 29863152; PMCID: PMC5881351.
11. Moris D, Rahnemai-Azar AA, Tsilimigras DI, Ntanasis-Stathopoulos I, Marques HP, Spartalis E, Felekouras E, Pawlik TM. Updates and Critical Insights on Glissonian Approach in Liver Surgery. J Gastrointest Surg. 2018 Jan;22(1):154-163. doi: 10.1007/s11605-017-3613-9. Epub 2017 Nov 3. PMID: 29101722.
12. Surjan RC, Makdissi FF, Machado MA. Anatomical basis for the intrahepatic glissonian approach during hepatectomies. Arq Bras Cir Dig. 2015 Apr-Jun;28(2):128-31. doi: 10.1590/S0102-67202015000200011. PMID: 26176251; PMCID: PMC4737336.
13. Qiu J, Chen S, Chengyou D. A systematic review of robotic-assisted liver resection and meta-analysis of robotic versus laparoscopic hepatectomy for hepatic neoplasms. Surg Endosc. 2016 Mar;30(3):862-75. doi: 10.1007/s00464-015-4306-7. Epub 2015 Jun 20. PMID: 26092026.
14. Giulianotti PC, Coratti A, Sbrana F, Addeo P, Bianco FM, Buchs NC, Annechiarico M, Benedetti E. Robotic liver surgery: results for 70 resections. Surgery. 2011 Jan;149(1):29-39. doi: 10.1016/j.surg.2010.04.002. Epub 2010 Jun 8. PMID: 20570305.
15. Spampinato MG, Coratti A, Bianco L, Caniglia F, Laurenzi A, Puleo F, Ettorre GM, Boggi U. Perioperative outcomes of laparoscopic and robot-assisted major hepatectomies: an Italian multi-institutional comparative study. Surg Endosc. 2014 Oct;28(10):2973-9. doi: 10.1007/s00464-014-3560-4. Epub 2014 May 23. PMID: 24853851.
16. Nishino H, Seo S, Hatano E, Nitta T, Morino K, Toda R, Fukumitsu K, Ishii T, Taura K, Uemoto S. What is a precise anatomic resection of the liver? Proposal of a new evaluation method in the era of fluorescence navigation surgery. J Hepatobiliary Pancreat Sci. 2021 Jun;28(6):479-488. doi: 10.1002/jhbp.824. Epub 2020 Oct 4. PMID: 32896953.
17. Handgraaf HJM, Boogerd LSF, Höppener DJ, Peloso A, Sibinga Mulder BG, Hoogstins CES, Hartgrink HH, van de Velde CJH, Mieog JSD, Swijnenburg RJ, Putter H, Maestri M, Braat AE, Frangioni JV, Vahrmeijer AL. Long-term follow-up after near-infrared fluorescence-guided resection of colorectal liver metastases: A retrospective multicenter analysis. Eur J Surg Oncol. 2017 Aug;43(8):1463-1471. doi: 10.1016/j.ejso.2017.04.016. Epub 2017 May 6. PMID: 28528189; PMCID: PMC5534212.
18. Marino MV, Di Saverio S, Podda M, Gomez Ruiz M, Gomez Fleitas M. The Application of Indocyanine Green Fluorescence Imaging During Robotic Liver Resection: A Case-Matched Study. World J Surg. 2019 Oct;43(10):2595-2606. doi: 10.1007/s00268-019-05055-2. PMID: 31222642.
19. Meloni MF, Chiang J, Laeseke PF, Dietrich CF, Sannino A, Solbiati M, Nocerino E, Brace CL, Lee FT Jr. Microwave ablation in primary and secondary liver tumours: technical and clinical approaches. Int J Hyperthermia. 2017 Feb;33(1):15-24. doi: 10.1080/02656736.2016.1209694. Epub 2016 Aug 2. PMID: 27416729; PMCID: PMC5235993.
20. Vidal-Jove J, Serres X, Vlaisavljevich E, Cannata J, Duryea A, Miller R, Merino X, Velat M, Kam Y, Bolduan R, Amaral J, Hall T, Xu Z, Lee FT Jr, Ziemlewicz TJ. First-in-man histotripsy of hepatic tumors: the THERESA trial, a feasibility study. Int J Hyperthermia. 2022;39(1):1115-1123. doi: 10.1080/02656736.2022.2112309. PMID: 36002243.
21. Mendiratta-Lala M, Wiggermann P, Pech M, Serres-Créixams X, White SB, Davis C, Ahmed O, Parikh ND, Planert M, Thormann M, Xu Z, Collins Z, Narayanan G, Torzilli G, Cho C, Littler P, Wah TM, Solbiati L, Ziemlewicz TJ. The #HOPE4LIVER Single-Arm Pivotal Trial for Histotripsy of Primary and Metastatic Liver Tumors. Radiology. 2024 Sep;312(3):e233051. doi: 10.1148/radiol.233051. PMID: 39225612; PMCID: PMC11427859.

Authors

Munya H. Talukder, MD, St. Elizabeth Medical Center, Brighton, MA.

Jenna Wilson, DO, St. Elizabeth Medical Center, Brighton, MA.

Andrew B. Crocker, MD, St. Elizabeth Medical Center, Brighton, MA.

Ali Ahmad, MD, FACS, University of Kansas School of Medicine, Wichita, KS.

Ponnandai Somasundar, MD, MPH, FACS, Boston University; Roger Williams Medical Center, Providence, RI.

Disclosures

None

Correspondence

Ponnandai Somasundar, MD

psomasun@bu.edu

Emerging Technologies for Pancreas Resection

JENNA WILSON, DO; MUNYA H. TALUKDER, MD; PONNANDAI SOMASUNDAR, MD, MPH; ALI AHMAD, MD, FACS

ABSTRACT

Pancreatic resection has necessitated continuous technological advancements since its first introduction into the surgical field. The delicate nature and complex anatomy of the pancreas demand an evolution of techniques to improve outcomes and lessen complications. This article serves as an overview of current and emerging surgical technologies that have helped to push the bar forward, broaden candidacy, and provide patients with better quality of life postoperatively. The topics of discussion include indications for pancreatic resection, as well as traditional pancreaticoduodenectomy and distal pancreatectomy, laparoscopic and robotic resection, ctDNA biomarkers, arterial divestment and autologous grafts, near infrared surgery, irreversible electroporation, and neo-adjuvant therapies.

KEYWORDS: Pancreatic resection; pancreaticoduodenectomy; robotic pancreatic surgery; near-infrared (NIR surgery); irreversible electroporation

INTRODUCTION

The surgical complexity of pancreatic resection remains a persistent challenge when it comes to advances in safety and favorable outcomes. As pancreatic cancer continues to be a lethal threat globally with a low five-year survival rate and tendency toward late detection, it is paramount that surgical options evolve and improve. The intricacies of pancreaticoenteric reconstruction and its associated morbidity have created an ongoing pursuit to develop technologies that combine the superior exposure and dexterity granted by an open resection with the advantages of minimally invasive techniques. Here we discuss the various existing approaches to pancreatic resection along with emerging adjuncts that are aiming to fill the gap between old and new.

INDICATIONS FOR PANCREATIC RESECTIONS

Pancreatic resection has amassed a reputation over the years that can lend itself to hesitancy from both the surgeon and patient perspective. Despite major advances in surgical technique and technology, pancreatic resection is still associated with a host of probable complications both immediate and long-term, simply due to the complexity of pancreatic anatomy and the unforgiving nature of the organ. Because of this, operative intervention for pancreatic pathology is reserved for strictly appropriate candidates. Some of the current indications for resection are described below.

Pancreatic adenocarcinoma

Though not the most common gastrointestinal malignancy, pancreatic cancer maintains the highest mortality rate of all major cancers and is the fourth leading cause of cancer deaths in the United States (US). It carries an estimated 8% five-year survival rate, with an overwhelming 85% of pancreatic cancers being represented by pancreatic adenocarcinoma.[1] Moreover, there is a tendency toward late detection of pancreatic adenocarcinoma due to its asymptomatic nature in the early stages, and by the time patients are diagnosed, only about 15–20% of them have resectable disease.[2] This means that they either have metastases or major vessel involvement, making resection unsafe or impossible. For those that do have resectable disease, the mainstay of treatment includes chemotherapy ± radiation and surgery.

Pancreatic neuroendocrine tumors

A rarer malignancy making up no more than 5% of pancreatic cancers is the pancreatic neuroendocrine tumor (PNET).[3] These are neoplasms of islet cell origin that can be classified as non-functional or functional. Functional PNETs include insulinomas, gastrinomas, glucagonomas, somatostatinomas, and VIPomas. The clinical manifestations differ depending on peptide secreted, which also plays into resection indications. In general, non-functional PNETs do require resection, as they have a high chance of malignancy. Since they are often asymptomatic until they are large enough to create a mass effect, these are frequently diagnosed at a late stage. On the other hand, the resection indications for functional PNETs vary depending on the size and features of the tumors. Insulinomas and gastrinomas can be managed with enucleation if they fit a favorable size and location category, vs formal resection if otherwise. Glucagonomas, somatostatinomas, and VIPomas typically require formal resection due to high malignancy potential.[3]

Intraductal papillary mucinous neoplasm

IPMNs are a benign pancreatic lesion that are known to have malignant potential. They are cystic, mucin-producing

neoplasms that grow within pancreatic ducts, and can undergo malignant transformation, making them potential precursors to pancreatic adenocarcinoma.[4] They are the most common pancreatic cystic lesion, making up about 50% of those diagnosed. Because of this, they are also the most common cystic neoplasm that undergoes resection.[5] Currently, prophylactic resection is recommended for all main duct IPMNs as well as branch duct IPMNs with high-risk features. The five-year survival rate after resection for noninvasive lesions is between 77–100%, while that of invasive carcinoma is 34–62%.[2, 6]

Serous cystadenoma/mucinous cystic neoplasms

Two other cystic neoplasms of the pancreas are serous cystadenoma and mucinous cystic neoplasms. Serous cystadenomas are reported to be the second most common pancreatic cystic lesion, followed by mucinous cystic neoplasms.[5] Since the vast majority are benign, resection is only indicated if they are greater than or equal to 4cm in size, symptomatic or obstructive, or growing on surveillance. Mucinous cystic neoplasms on the other hand, have a higher chance of malignancy, up to 25%, and resection is indicated.[5]

Chronic Pancreatitis

Patients who experience chronic pancreatitis endure a host of potentially debilitating symptoms that can extend beyond what medical management can provide. From severe abdominal pain, to ongoing fibrosis of both pancreatic tissue and adjacent organs, to impairment of endocrine and exocrine function, the wide range of manifestations can require operative intervention.[7] The most common indication for surgery in chronic pancreatitis is refractory pain due to pancreatic duct obstruction. The procedures offered typically involve resection, drainage, or a combination of both. Multiple randomized control trials have shown surgical management of chronic pancreatitis to be superior to endoscopic drainage in terms of pain relief.[8, 9] One of which demonstrated 75% of patients with partial or complete pain relief after surgery as compared to 30% after endoscopic drainage.[8]

TRADITIONAL TECHNIQUES OF PANCREATIC SURGERY: A BRIEF HISTORY

Commonly regarded as the birth of pancreatic surgery, the first successful major pancreatic resection was performed by Dr. Friedrich Trendelenburg in 1882. He performed a distal pancreatectomy for a large solid mass arising from the tail of the pancreas, and while the patient did sustain a splenic injury requiring splenectomy and died several weeks later from what was presumed to be respiratory failure, the procedure itself was technically successful and became an important landmark in the history of pancreatic surgery.[2] Several decades and daring surgeons later, Dr. Allen Whipple developed a two-stage procedure in 1935 for the radical resection of periampullary tumors which involved common bile duct ligation, cholecystogastrostomy, and posterior loop gastrojejunostomy, followed by partial duodenectomy and pancreatic head resection.[2] He later revised this and ultimately condensed it into a one-stage procedure during a 1940 case in which the patient was found intraoperatively to have a pancreatic head mass and lived for nine more years following her surgery. This technique was then refined into the pancreaticoduodenectomy, or "Whipple procedure" that we know today. Variations of this procedure are currently used for pancreatic head masses, periampullary tumors, severe pancreatic trauma, and more.

SURGICAL APPROACHES

Pancreaticoduodenectomy

The pancreaticoduodenectomy, inclusive of the classic Whipple procedure as well as pylorus sparing variations, is indicated for masses of the head of the pancreas, and bile duct and periampullary tumors. It consists of several key components, including bilioenteric reconstruction comprised of three anastomoses: pancreaticojejunostomy, hepaticojejunostomy, and gastrojejunostomy.[10] It is a complicated procedure that requires both careful patient selection and surgeon experience for favorable outcomes. It has been reported that the mortality of this procedure at high-volume centers is less than 1–2%, but morbidity remains high at 30–45% of patients. In patients with resectable disease, it has been shown to improve five-year mortality to about 15–25%.[11]

Distal pancreatectomy

Distal pancreatectomy is indicated for tumors of the body and tail of the pancreas. Due to the anatomic proximity to the spleen, this is often performed in conjunction with a splenectomy, though a spleen-preserving variation can also be performed. Because resection of this portion of the pancreas does not require complex bilioenteric reconstruction, it is associated with a lower morbidity and mortality.

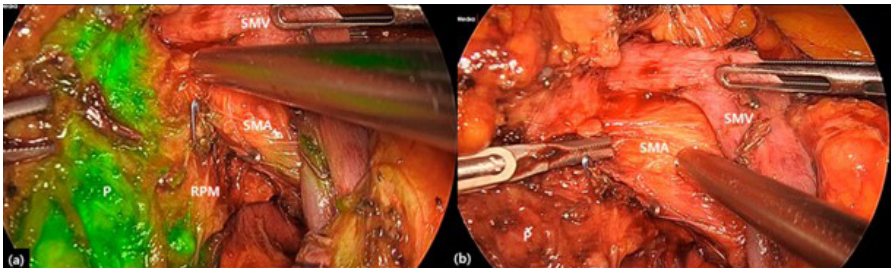
MINIMALLY INVASIVE TECHNIQUES

Laparoscopic resection

Advances in laparoscopy have been one of the most important factors in widening the candidacy for pancreatic surgery. The main advantages of laparoscopic resection over traditional open techniques include reduced intraoperative blood loss, reduced postoperative pain, and shorter length-of-stay (LOS). A meta-analysis examining six RCT on the topic of open vs minimally invasive pancreatic surgery demonstrated that the minimally invasive group had an average of 1.3 days shorter LOS, as well as 137ml less blood loss when compared to the open group.[12] This also demonstrated fewer surgical site infections. On the other hand, the same analysis revealed a longer operative time, about 54 minutes

on average, for laparoscopic cases, highlighting the difficulty of the technique.[12] Overall, laparoscopic pancreatic resection has been found to be successful at high volume centers, but requires technically outstanding laparoscopists. Pancreaticoenteric anastomoses are complex surgical entities and remain a major source of morbidity even at the hands of experienced surgeons at tertiary centers.[13]

Figure 1. Intraoperative usage of ICG during pancreatic resection. The stained area is pancreatic tissue (the uncinate process), which is visually differentiated from the SMA and SMV, aiding in resection margins.[16]



Robot-assisted resection

The surgical robot solves several technical issues that traditional laparoscopy creates, from 3D visualization, to wide-ranging wrist articulation, to improved ergonomics. These advances have helped to overcome major roadblocks with laparoscopic pancreatic resection.[13] While little high powered data exists for direct comparison of laparoscopic vs robotic-assisted resection (RA), the studies we do have demonstrate the RA approach has less conversion to open surgery, and even less excessive blood loss. RA also has better oncologic outcomes with higher rates of margin negative resection and improved lymph node yield for both benign and malignant lesions.[13] However, as with any emerging technology, there is a significant learning curve to the robotic approach. This same meta-analysis also reported on the comparison of learning curve time for laparoscopic vs robotic resection, and found an average of 30 cases vs 36.5 respectively.[13]

Minimally invasive in comparison to open resection

Overall, minimally invasive techniques, whether laparoscopic or robotic, have comparable morbidity and mortality to open resection. The main advantages of open resection include a shorter operative time due to the lack of laparoscopic technical complexity, and the superior haptic feedback that open surgery provides.

EMERGING TECHNIQUES/INTRAOPERATIVE ADJUNCTS

As more surgeons are trained in minimally invasive techniques for pancreatic surgery, the next frontier to conquer is the adjunct technologies that can make these approaches even more efficient and effective. Some of these technologies are described below.

Near-Infrared (NIR) surgery

One major advantage of the minimally invasive approach to pancreatic resection is the ability to use tumor localizing dye to help guide resection. Indocyanine green (ICG) is a fluorescent dye that is given intravenously and binds to plasma proteins and remains intravascular before being cleared by hepatocytes and secreted into bile. Using an NIR camera intraoperatively after ICG administration allows for visualization of the biliary tree, various vascular structures, tumors and metastatic deposits [**Figure 1**].[14] A 2022 systematic review and meta-analysis demonstrated that the use of ICG can help surgeons identify pancreatic lesions with an accuracy of 81.3%.[14] Another study titled, *The COLPAN Study (Colour and Resect the Pancreas)* 2017, studied subjects undergoing minimally invasive resection of pancreatic neuroendocrine tumors who were injected with ICG dye to help identify lesions intraoperatively. Nine out of 10 PNETs were identified after the second bolus of ICG.[15]

Reconstructive techniques for tumors with vascular involvement

When discussing the resectability of a pancreatic tumor, an important criterion to know is the vascular involvement of the tumor. Generally speaking, if the tumor involves a major venous structure, it can still be considered borderline resectable if venous reconstruction is possible. If it has less than 180 degrees of abutment with the celiac axis or SMA, it is considered borderline resectable, and greater than 180 degrees of abutment is considered locally advanced.[17] However, development of vascular reconstructive techniques has allowed for a greater number of these tumors to be resected.

Some pancreatic tumors, particularly pancreatic ductal adenocarcinoma (PDAC), infiltrate the nerve fibers and soft tissue that surround the celiac axis, common hepatic artery, and SMA, without actually involving the arterial walls themselves.[17] This is an important distinction to make, as a true involvement of the wall requires resection, which carries a high morbidity and mortality rate. For those tumors that involve the periarterial tissue only, arterial divestment can be attempted. This is essentially a meticulous dissection of the periadventitial plane between the tumor and the artery itself, allowing for an R0 resection without needing to do any resection or reconstruction [**Figure 2**].[18]

Graft reconstruction

For those tumors that do have true involvement beyond the adventitia of these major arterial structures, surgeons have

Figure 2: Sub-adventitial divestment of a grade I tumor with invasion into the tunica adventitia.[19]

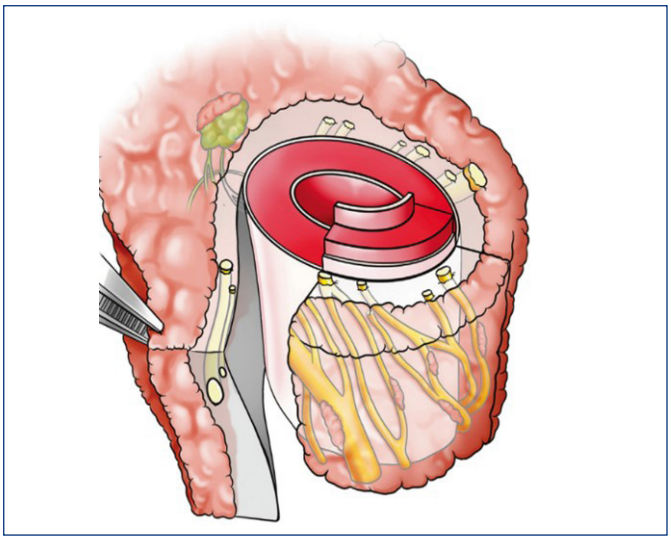
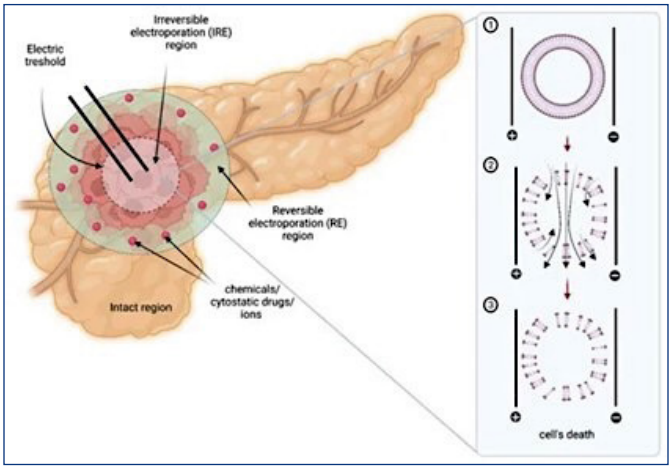


Figure 3: Irreversible electroporation electrodes surrounding pancreatic tumor.[23]



the option of using autologous or synthetic grafts to reconstruct the vessels that require resection. In certain cases with short segment involvement, end-to-end anastomosis can be performed, but most patients undergoing arterial resection will require an interposition graft. Several autologous options exist, including harvested saphenous or renal veins, or splenic artery if splenectomy is also being performed.[17] Synthetic grafts can also be used, though care must be taken in these cases to avoid graft infection.[17] Though these techniques have evolved and improved over the years, arterial resection and reconstruction remain significant sources of morbidity and mortality in pancreatic resections, with one study citing a 90-day major morbidity rate of 53% and mortality rate of 14%.[20] Most of these complications were due to postoperative hemorrhage, pancreatic fistula, or ischemia.[20]

Irreversible electroporation (IRE)

So far, our discussion has focused primarily on operative strategies for resectable disease. However, a significant subsect of patients have unresectable disease without arterial reconstruction options. One treatment modality under development for these patients is irreversible electroporation (IRE). This strategy involves an ablation technique that uses high voltage, low energy electropulsations to create pores in the tumor cell membranes, leading to necrosis [**Figure 3**]. Because this is a non-thermal technique, there is no risk of thermal injury to surrounding areas, making it a theoretically safe approach for tumors close to vital structures.[21] This technique is particularly useful for margin accentuation, or the treatment of tumor edges in order to decrease the likelihood of leaving positive tumor margins behind.[22] The efficacy of this technique has been demonstrated in vivo and in vitro studies. While the technology is promising, one major disadvantage of IRE is its inability to eradicate larger tumors >3cm. This is potentially due to the fact that the electrodes would need to be further away from the core of the target tissue, leading to a decreased magnitude of pulsation reaching each part of the mass.[22] Regardless of this, IRE remains an exciting territory for treatment of pancreatic malignancies, even if only as an adjunct to surgical resection.

FUTURE DIRECTIONS

Despite all of the impressive advancements discussed above, the final frontier of successful treatment of pancreatic cancer is early detection of disease. Currently, the majority of pancreatic cancers are discovered only after symptoms have manifested and disease is more likely to be at least locally advanced at that time. Some sources estimate up to 85% of diagnosed PDACs are locally advanced or metastatic at the time of diagnosis.[20]

An emerging area of interest for early detection is the "liquid biopsy" or body fluid sample such as blood, saliva, or urine, that may contain biomarkers that can direct a diagnosis of pancreatic cancer. One such biomarker being examined is circulating cell-free tumor DNA (ctDNA). This approach looks for circulating nucleic acids of tumor cells that are prevalent during early stage disease, which could provide diagnosis without the undue risk of tissue biopsy.[20] While the concept is promising for future development, ctDNA testing is currently somewhat controversial as a method for early detection of pancreatic cancer due to its instability, low circulating volume, and variable sensitivity and specificity across available studies.[20]

Another encouraging area undergoing development is neoadjuvant chemotherapy for pancreatic cancer. Currently, some data supports that a course of neoadjuvant chemotherapy can improve 12-month overall survival rates to 77% compared to 40% in the upfront surgery groups.[24] This

data also shows that it can make patients with previously unresectable cancers newly eligible for surgery, as well as improve the overall survival of those who experience postoperative complications.[24]

CONCLUSION

As new technologies emerge to help solve problems in the operating room, an additional problem is created: where do these technologies fit in with existing techniques and how can they be incorporated to improve outcomes as well as efficiency? The advent of the surgical robot has moved the needle forward dramatically in terms of creating a more ergonomic operating environment with improved visualization without needing to commit patients to the complications associated with open surgery; however, we continue to seek out additional tools that can be used along with the robot that can push it to be unequivocally superior for safety and outcomes. The adjuncts discussed here have indeed broadened surgical candidacy and therefore allowed more patients to lead longer and more comfortable lives, which is the ultimate purpose of this work.

References

1. Patel N, Khorolsky C, Benipal B. Incidence of Pancreatic Adenocarcinoma in the United States from 2001 to 2015: A United States Cancer Statistics Analysis of 50 States. Cureus. 2018 Dec 28;10(12):e3796. doi: 10.7759/cureus.3796. PMID: 30868010; PMCID: PMC6402725.
2. Griffin JF, Poruk KE, Wolfgang CL. Pancreatic cancer surgery: past, present, and future. Chin J Cancer Res. 2015 Aug;27(4):332-48.
3. Batcher E, Madaj P, & Gianoukakis A. G. Pancreatic Neuroendocrine Tumors. Endocrine Research. 2011;36(1):35–43.
4. Puckett Y, Sharma B, Kasi A. Intraductal Papillary Mucinous Neoplasm of the Pancreas. [Updated 2023 Aug 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507779/
5. Karoumpalis I, Christodoulou DK. Cystic lesions of the pancreas. Ann Gastroenterol. 2016 Apr-Jun;29(2):155-61.
6. Tanaka M, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas, Pancreatology. 2012;12(3):183-197
7. Stefan A, et al. Dutch Pancreatitis Study Group; Surgery in Chronic Pancreatitis: Indication, Timing and Procedures. Visc Med 2019;35(2):110–118.
8. Cahen D, et al. Endoscopic versus Surgical Drainage of the Pancreatic Duct in Chronic Pancreatitis. NEJM 2007;7(15):676–684
9. Dite P, et al. A Prospective, Randomized Trial Comparing Endoscopic and Surgical Therapy for Chronic Pancreatitis. Endoscopy 2003;35(7):553–558
10. D'Cruz JR, Misra S, Menon G, et al. Pancreaticoduodenectomy (Whipple Procedure) [Updated 2024 Oct 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560747/
11. Giuliano K, Ejaz A, & He J. (2017). Technical aspects of pancreaticoduodenectomy and their outcomes. Chinese Clinical Oncology 2017;6(6):64.
12. Pfister M, et al. Minimally invasive versus open pancreatic surgery: meta-analysis of randomized clinical trials, BJS Open 2023; 7(2): zrad007
13. Zureikat A, Nguyen K, Bartlett D, Zeh H, Moser A. Robotic-Assisted Major Pancreatic Resection and Reconstruction. Arch Surg. 2011;146(3):256–261.
14. Rompianesi G, et al. Systematic review, meta-analysis and single-centre experience of the diagnostic accuracy of intraoperative near-infrared indocyanine green-fluorescence in detecting pancreatic tumours, HPB 2022;24(11):1823-1831
15. Paiella S, et al. Is there a role for near-infrared technology in laparoscopic resection of pancreatic neuroendocrine tumors? Results of the COLPAN "colour-and-resect the pancreas" study. Surg Endosc 2017;31:4478–4484
16. Is Laparoscopic Pancreaticoduodenectomy Feasible for Pancreatic Ductal Adenocarcinoma? - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Intraoperative-usage-of-indocyanine-green-ICG-during-obtaining-the-retroperitoneal_fig2_347307019 [accessed 14 Mar 2025]
17. Schneider M, Hackert T, Strobel O, Büchler M, Technical advances in surgery for pancreatic cancer, British Journal of Surgery 2021:108(7):777–785
18. Markus K, et al. Periarterial divestment in pancreatic cancer surgery. Surgery 2021;169(5):1019-1025.
19. Cai Baobao, et al. Sub-adventitial divestment technique for resecting artery-involved pancreatic cancer: a retrospective cohort study. Langenbeck's Archives of Surgery 2021;406 (3):691-701.
20. Jaworski J, Morgan R, Sivakumar S. Circulating Cell-Free Tumour DNA for Early Detection of Pancreatic Cancer. Cancers (Basel) 2020; 12(12):3704.
21. Gajewska-Naryniecka A, et al. Irreversible Electroporation in Pancreatic Cancer-An Evolving Experimental and Clinical Method. Int J Mol Sci. 2023;24(5):4381.
22. Ratnayake B, et al. Margin Accentuation Irreversible Electroporation in Stage III Pancreatic Cancer: A Systematic Review. Cancers (Basel). 2021;13(13):3212.
23. Wasson E, et al. The Feasibility of Enhancing Susceptibility of Glioblastoma Cells to IRE Using a Calcium Adjuvant. Ann. Biomed. Eng. 2017;45:2535–2547.
24. Springfeld C, et al. Neoadjuvant therapy for pancreatic cancer. Nat Rev Clin Oncol 2023;20:318–337 (2023).

Authors

Jenna Wilson, DO, St. Elizabeth Medical Center, Brighton, MA .

Munya H. Talukder, MD, St. Elizabeth Medical Center, Brighton, MA.

Ponnandai Somasundar, MD, MPH, FACS, Boston University; Roger Williams Medical Center, Providence, RI.

Ali Ahmad, MD, FACS, University of Kansas School of Medicine, Wichita, KS.

Disclosures

None

Correspondence

Ali Ahmad, MD, FACS
Wichita Surgical Specialists – Emporia
818 North Emporia Ave., Ste. 200
Wichita, KS 67214
316-263-0296

Management of Benign Symptomatic Thyroid Nodules in Rhode Island Using Radiofrequency Ablation

NINA S. LI, BS; SONIA GIYANANI, DO; DAEHEE KIM, MD; STEVE KWON, MD, MPH; JOHN LEE, MD

ABSTRACT

The management of benign symptomatic thyroid nodules can pose a challenge when weighing treatment options. While surgical resection has been the gold standard, the risks and consequences of partial or total thyroidectomy may outweigh the benefits of the procedure. Additionally, a significant number of patients are not surgical candidates due to comorbidities, potential risks, or personal preference. Radiofrequency ablation (RFA) has emerged as a minimally invasive, low-risk alternative to traditional surgery, and it has demonstrated to have high efficacy in nodule volume reduction, symptom resolution, and cosmetic improvement. Hence, the use of RFA for treatment of benign thyroid nodules has been supported by both international and national professional groups. This paper hopes to promote the use of RFA for treatment of benign solid thyroid nodules in the Rhode Island population as well as outline its potential clinical application.

KEYWORDS: Radiofrequency ablation; benign symptomatic thyroid nodule; minimally invasive procedure

INTRODUCTION

There is a high prevalence of thyroid nodules in the general population, with an upwards of 50–60% detection.[1] The majority of thyroid nodules are found from incidental findings and benign. Hence, management includes ruling out potential malignancy (5–15% of cases)[2,3] and treatment of nodules causing significant symptoms and/or cosmetic concerns. Symptoms of a thyroid nodule can include dysphagia, dyspnea, foreign body sensation, voice change, and cough.[4] In addition, toxic nodules producing hormone dysfunction and thyrotoxicosis are often an indication for treatment.

Surgical resection has been the gold standard for treatment of clinically significant benign thyroid nodules. Partial or total thyroidectomy poses certain risks and complications including transient hypocalcemia (~5–20%),[5] permanent hypocalcemia (<3%),[5] persistent hypoparathyroidism (~2%),[6] recurrent or superior laryngeal nerve injury (1–4%),[6] hemorrhage (~2%).[7] The incidence of post hemithyroidectomy hypothyroidism has been reported to be approximately 27%, indicating that a significant portion of patient will require thyroid hormone therapy.[8] These risks and complications often outweigh the benefits of the procedure, especially in patients with benign disease. Therefore, there has been an increased interest towards alternative minimally invasive procedures. Specifically, radiofrequency ablation (RFA) has garnered great interest due to its increased efficacy in comparison to other ablation treatments.[9]

RFA is a minimally invasive, low-risk procedure that utilizes an electrode under sonographic guidance to treat the target thyroid nodule. RFA has been endorsed in guidelines by multiple national, professional societies as a promising alternative to surgery for patients with benign symptomatic thyroid nodules and/or with malignant disease who are not surgical candidates.[1,10] International groups including the Korean Society of Thyroid Radiology and European Thyroid Association also share similar sentiments in recent guidelines for use of RFA for clinically significant benign thyroid nodules.[11-15] This article hopes to describe the potential impact of RFA as a low-risk and cost-effective alternative for the treatment of benign solid thyroid nodules in select patients in the state of Rhode Island.

CURRENT PRACTICE GUIDELINES

Various professional groups have supported the use of RFA for treatment of benign symptomatic thyroid nodules, and as such, there are agreements as well as variations in specific practice guidelines outlined. The Asian Conference on Tumor Ablation (ACTA) Task Force consolidated recommendations and highlighted areas of debate from recommendations made by academic societies in various countries.[13] For benign, nonfunctioning thyroid nodules with symptoms or cosmetic concerns, a 10 cm Visual Analog Scale for symptoms and cosmetic score (a cosmetic score of 1 to 4: (1) no palpable mass, (2) no cosmetic issues but a palpable mass, (3) cosmetic issue only during swallowing, and (4) nodule visible to the naked eye) can be utilized to assess patient burden and the need for treatment.[13] While there are no definitive cutoff values for nodule size, nodules exceeding a maximum diameter of 2 cm and demonstrating continued growth may be considered for RFA treatment if they pose symptoms, cosmetic and/or clinical concerns.[11] Historically, cytologically benign nodules of 4 cm or larger were recommended for surgical removal due to increased risk of

carcinoma development, structural and/or compressive concerns, as well as cosmetic concerns, but modern approaches rely more on assessment of symptoms and changes over time as smaller nodules can also cause concerns depending on nodule location and patient neck circumference.[11,16]

THE RADIOFREQUENCY ABLATION PROCEDURE

The thyroid nodule should be confirmed to be benign by at least two ultrasound-guided fine needle aspiration (FNA) or core needle biopsy (CNB) prior to RFA to prevent possible false-negative diagnosis of malignancy.[13] However, some guidelines believe a single diagnosis of a thyroid nodule with highly suggested benign features (isoechoic spongiform or partially cystic nodules with an intra-cystic comet tail artifact) is sufficient.[11] On ultrasound, the following are evaluated in detail to determine if the nodule may be suitable for RFA: nodule echogenicity, margin, vascularity, volume, and relationship of nodule to surrounding critical structure. The following labs are also reviewed: complete blood count, coagulation test, thyroid function test, and thyroid autoantibodies if thyroid function test abnormality is present.[13]

RFA procedure consists of inserting a probe connected to a generator producing a high-frequency current into the target nodules. The resulting heat produced due to the electrical current passing through a circuit with focal impedance (i.e., the target tissue) induces thermal injury and coagulative necrosis in the target tissue.[4] The procedure is generally performed under local anesthesia and real-time sonography guidance; general anesthesia is not recommended.[13] Treated areas will appear as mildly hypoechoic spots on ultrasound, demonstrating tissue vaporization. There are several important techniques employed with thyroid RFAs to reduce complications related to thermal damage to surrounding structures. First, hydro-dissection technique is used to protect adjacent surrounding structures of the neck. The hydro-dissection technique involves injection of either lidocaine or dextrose 5% in water in between the nodule and critical adjacent structures (e.g., carotid artery, recurrent laryngeal nerve), creating a margin of safety that prevents unintentional thermal damage.[11,17] Second, the "moving-shot" technique through the trans-isthmic approach has been employed to treat thyroid nodules, where the electrode tip is moved continuously to ensure adequate treatment coverage and adequate sonographic target visualization while preventing overtreatment of the peripheral margins.[13] The electrode needle can be inserted in the midline-to-lateral direction first at the deepest and most remote portion of the nodule, and then gradually moved backwards for best electrode visualization and control.[13]

Follow-up visits are recommended at one to three months for early exam of initial effects of ablation and for thyroid function analysis, at six and twelve months for assessment of volume reduction as this is where max nodule shrinkage is obtained, and at every six to twelve months thereafter to monitor for regrowth.[12,13] In certain cases, including marginal regrowth of the treated nodules, increase of 50% volume compared to minimum recorded volume, <50% volume reduction rate, or incomplete resolution of symptoms, additional rounds of RFA may be considered.

PATIENT SELECTION AND ELIGIBILITY

RFA should be used for the treatment of solid or majority solid benign thyroid nodules causing symptomatic, clinical, or cosmetic concern. RFA should not be performed on nodules with high-risk ultrasound features due to risk of harboring malignancy, and unnecessary treatment of asymptomatic benign nodules are discouraged.[12] RFA can be the treatment of choice for autonomously functioning thyroid nodules (AFTNs) in instances where the patient refuses both surgery and radioactive iodine treatment. Additionally, it can be considered for cases of AFTN in young patients due to the potential of a much longer period of hypothyroidism following RAI or surgery.[4] RFA has demonstrated to have lower efficacy in larger nodules, and therefore nodules >20 mL in volume are not recommended for RFA treatment.[11] Selected cases of malignant thyroid nodule, such as residual or recurrent disease after thyroidectomy can be considered for RFA after multidisciplinary discussion. Indications for RFA of malignant nodules rather than surgical resection may be appropriate in cases where the patient is a nonsurgical candidate and the tumor is of specific locations (unifocal disease, central location in gland, confined to thyroid gland) or types.[4,10] Bipolar electrode may be recommended for pregnant women or patients with cardiac pacemaker.[13] Imaging from a benign thyroid nodule RFA procedure at Roger Williams Medical Center is shown in **Figure 1**.

OUTCOMES OF THYROID NODULE RADIOFREQUENCY ABLATION

Benign thyroid nodules compromise a high impact area of RFA. RFA has been widely adopted across Asia and Europe over the past decade for treatment of benign nodules. In international studies, there is an overall consensus in the literature suggesting RFA to be efficacious in reducing nodule volume, with 70% to 80% reduction in six to 18 months or even higher depending on the study, as well as improving related symptoms and cosmetic concerns.[18-22] Therapeutic response is often defined as >50% volume reduction after twelve months. A retrospective cohort study comparing outcomes of RFA to surgery for treatment of benign thyroid nodules found that RFA reduced nodular volume by 70% after 12 months and was more cost-effective than surgery for the treatment of nodule-related clinical problems.[22] A large systematic review of reports published between 2009 and 2021 of mostly solid nodules found that volume reduction at

Figure 1A,B. Pre-procedure imaging of a 2.9 x 2 x 2.8 cm TIRADS 4 right thyroid nodule with two fine needle aspiration results showing benign findings. Patient had symptoms of dysphagia and cosmetic concerns.

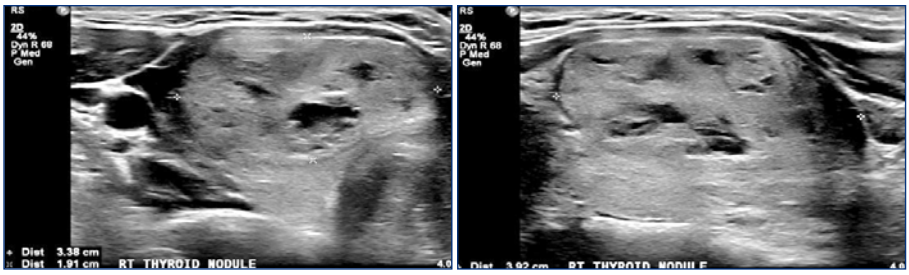
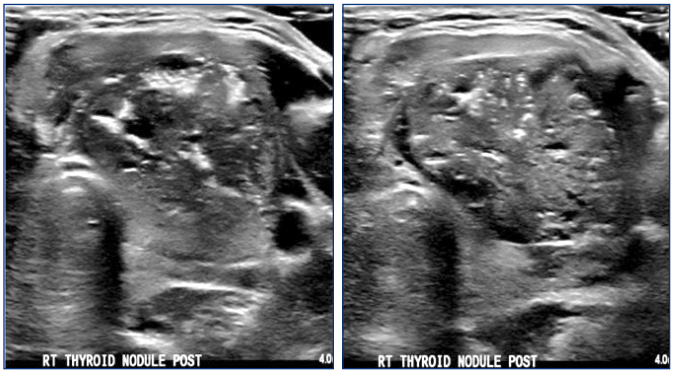


Figure 1C,D. Post-procedure imaging demonstrating post radiofrequency ablation changes including areas of hyperechogenicity without evidence of immediate complications.



12 months follow-up ranged from 67 to 75% for single treatment nodules and reached approximately 94% for repeat treatments, demonstrating that RFA produced long-term clinical efficacy.[18]

The FDA-approved use of RFA in soft tissue tumors in 2018, and since US-based studies have also found RFA to be efficacious in treatment of benign thyroid nodules. For large benign thyroid nodules, defined as 3 cm in largest diameter, an early case series by Mayo Clinic found a median volume reduction rate (VRR) of 44.6% over a median follow up of 8.6 months.[23] Subsequent studies in the US also found significant VRRs and good efficacy. A single center retrospective study between 2018 and 2021 found that mean VRR was 70.8% after a median follow-up period of 109 days, with symptomatic and cosmetic improvement ($P < 0.01$).[24] Both nonfunctioning thyroid nodules (NFTNs) and AFTNs were included in the study, and RFA was found to cause a greater volume reduction in smaller nodules ($P = 0.03$) and improve thyrotropin (TSH) in AFTNs (P value < 0.01).[25] A study at Columbia University saw that RFA procedures performed in the outpatient setting under local anesthesia were well tolerated and resulted in a VRR of 52.9% at one month follow-up.[21] All patients included in the study (n = 15), except two, had nodules that were benign on fine-needle biopsy but enlarging, symptomatic, or toxic, and patients were euthyroid at follow up, suggesting reduced need of thyroid hormone supplementation compared to traditional surgery.[8]

Several studies have also reported on the positive improvements of cosmetic and symptoms scores following RFA. A US-based study following 56 patients with 76 benign thyroid nodules treated with RFA demonstrated a significant improvement for goiter symptoms, anxiety, appearance, and quality of life at 12-month follow-up ($P< 0.05$).[26] Additionally, in a cohort of 94 elderly patients with cytologically benign compressive thyroid nodules, relief of compressive symptoms were found in 88% of patients.[27] Pooled measures of mean symptomatic score and cosmetic score from 14 and 12 available studies, respectively, demonstrated a decreased postoperative symptomatic score (3.83 vs 1.09) and cosmetic score (3.43 vs 1.51), providing further support for the efficacy of RFA in treating benign thyroid nodules for symptomatic and cosmetic indications.[11]

RFA is predominantly indicated for solid or predominantly solid benign thyroid nodules. Moderate efficacy has been demonstrated by RFA in treating toxic thyroid nodules with a 57% TSH normalization rate and 79% VRR at one year.[28] Other nodule subtypes including benign AFTNs, cystic nodules and malignant nodules may not be as effectively resolved with RFA compared to current standard treatments (e.g., RAI, ethanol ablation, surgery, respectively) and should only be treated in the case that the patient denies or is unsuited for surgery or RAI, or where the risks of hypothyroidism may be too detrimental.[4,11,12,19] While RFA and ethanol ablation have been demonstrated to have similar outcomes, the lower cost and superior safety profile of ethanol ablation indicates it as the preferred treatment for cystic nodules.[4]

SAFETY AND OTHER CONSIDERATIONS

RFA is generally well tolerated with low complications rates of around 3.3%.[29] Minor complications can include mild hematoma, postoperative transient hoarseness, mild pain, and skin burn; major complications, although rare, can include permanent voice change, brachial plexus injury, recurrent laryngeal nerve injury, nodule rupture, and permanent hypothyroidism.[29,30] However, generally when compared to surgery, RFA produces significantly lower incidence of complications than surgery (6.0% vs 1.0%, P= 0.002), lower rates of residual nodules (11.9% versus 2.9%, P = .004), reduced hospitalization days, and preservation of thyroid function.[24] Following RFA treatment for benign NFTNs, it has also been shown that while there is transient relative hypothyroidism and increase in thyroid antibodies,

the levels normalize within 12 months with most rises in TSH remaining in normal range.[31] Long-term follow-up will be necessary to monitor potential regrowth.

Multiple factors including ill-defined margins, large nodule size, functional autonomy, and low applied energy can affect the successfulness of RFA treatment as well as potentiation for nodule regrowth after treatment.[12,22] Regrowth rates can range from 0–34%, as demonstrated by a recent systematic review of data published between 2008 and 2021.[18] There is also reduced efficacy of RFA in larger nodules (>20 mL) and variable rate of thyroid function normalization for AFTN.[11] In past studies following patients treated for non-functioning thyroid nodules with RFA for over three years, 24–60% of cases required more than two sessions of RFA to maintain long-term volume reduction.[11] Therefore, while RFA causes expected decrease in nodule size, patients should be informed that there is not complete disappearance of the nodule and additional treatment or surgery may be necessary if there is subsequent regrowth.[13]

CONCLUSION AND LOOKING FORWARD

Radiofrequency ablation is an attractive alternative to conventional surgery for the treatment of benign thyroid nodules. With low complication rates, short procedure and recovery time, reduced cost, and efficacy in treating symptomatic benign thyroid nodules, it can serve as a great option for patients who are not great surgical candidates or who refuse surgery. RFA also greatly diminishes the risk of hypothyroidism and need for life-long hormone supplementation. Patient workup includes diagnostic thyroid ultrasound, clinical work up, and fine needle aspiration to rule out potential malignancy. Treatment of thyroid nodules posing no symptomatic or aesthetic concerns is not advised. With the proven safety and efficacy of RFA for treatment of benign thyroid nodules, we believe that this technique would be a great treatment option for patients in the state of Rhode Island.

References

1. Gharib H, Papini E, Garber JR, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules - 2016 Update Appendix. *Endocr Pract*. 2016;22:1-60. doi:10.4158/EP161208.GL
2. Kamran SC, Marqusee E, Kim MI, et al. Thyroid Nodule Size and Prediction of Cancer. *J Clin Endocrinol Metab*. 2013;98(2):564-570. doi:10.1210/jc.2012-2968
3. Smith-Bindman R, Lebda P, Feldstein VA, et al. Risk of Thyroid Cancer Based on Thyroid Ultrasound Imaging Characteristics: Results of a Population-Based Study. *JAMA Intern Med*. 2013;173(19):1788-1796. doi:10.1001/jamainternmed.2013.9245
4. Navin PJ, Thompson SM, Kurup AN, et al. Radiofrequency Ablation of Benign and Malignant Thyroid Nodules. *RadioGraphics*. 2022;42(6):1812-1828. doi:10.1148/rg.220021
5. Christou N, Mathonnet M. Complications after total thyroidectomy. *J Visc Surg*. 2013;150(4):249-256. doi:10.1016/j.jviscsurg.2013.04.003
6. Rosato L, Avenia N, Bernante P, et al. Complications of Thyroid Surgery: Analysis of a Multicentric Study on 14,934 Patients Operated on in Italy over 5 Years. *World J Surg*. 2004;28(3):271-276. doi:10.1007/s00268-003-6903-1
7. Farooq M, Nouraei R, Kaddour H, Saharay M. Patterns, timing and consequences of post-thyroidectomy haemorrhage. *Ann R Coll Surg Engl*. 2017;99(1):60-62. doi:10.1308/rcsann.2016.0270
8. Miller FR, Paulson D, Prihoda TJ, Otto RA. Risk Factors for the Development of Hypothyroidism After Hemithyroidectomy. *Arch Otolaryngol Neck Surg*. 2006;132(1):36-38. doi:10.1001/archotol.132.1.36
9. Ha EJ, Baek JH, Kim KW, et al. Comparative Efficacy of Radiofrequency and Laser Ablation for the Treatment of Benign Thyroid Nodules: Systematic Review Including Traditional Pooling and Bayesian Network Meta-analysis. *J Clin Endocrinol Metab*. 2015;100(5):1903-1911. doi:10.1210/jc.2014-4077
10. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid®*. 2016;26(1):1-133. doi:10.1089/thy.2015.0020
11. Kim J, Baek JH, Lim HK, et al. 2017 Thyroid Radiofrequency Ablation Guideline: Korean Society of Thyroid Radiology. *Korean J Radiol*. 2018;19(4):632-655. doi:10.3348/kjr.2018.19.4.632
12. Papini E, Monpeyssen H, Frasoldati A, Hegedüs L. 2020 European Thyroid Association Clinical Practice Guideline for the Use of Image-Guided Ablation in Benign Thyroid Nodules. Published online July 1, 2020. doi:10.1159/000508484
13. Ha EJ, Baek JH, Che Y, et al. Radiofrequency Ablation of Benign Thyroid Nodules: Recommendations from the Asian Conference on Tumor Ablation Task Force – Secondary Publication. *J Med Ultrasound*. 2021;29(2):77-83. doi:10.4103/JMU.JMU_178_20
14. Papini E, Pacella CM, Solbiati LA, et al. Minimally-invasive treatments for benign thyroid nodules: a Delphi-based consensus statement from the Italian minimally-invasive treatments of the thyroid (MITT) group. *Int J Hyperthermia*. 2019;36(1):375-381. doi:10.1080/02656736.2019.1575482
15. Dobnig H, Zechmann W, Hermann M, et al. Radiofrequency ablation of thyroid nodules: "Good Clinical Practice Recommendations" for Austria. *Wien Med Wochenschr*. 2020;170(1):6-14. doi:10.1007/s10354-019-0682-2
16. Alexander EK, Doherty GM, Barletta JA. Management of thyroid nodules. *Lancet Diabetes Endocrinol*. 2022;10(7):540-548. doi:10.1016/S2213-8587(22)00139-5
17. Kuo JH, Lee JA. The Adoption of Ultrasound-guided Radiofrequency Ablation of Thyroid Nodules in the United States. *Ann Surg*. 2021;273(1):e10. doi:10.1097/SLA.0000000000003930
18. Monpeyssen H, Alamri A, Ben Hamou A. Long-Term Results of Ultrasound-Guided Radiofrequency Ablation of Benign Thyroid Nodules: State of the Art and Future Perspectives—A Systematic Review. *Front Endocrinol*. 2021;12. doi:10.3389/fendo.2021.622996
19. Bernardi S, Dobrinja C, Fabris B, et al. Radiofrequency Ablation Compared to Surgery for the Treatment of Benign Thyroid Nodules. *Int J Endocrinol*. 2014;2014:934595. doi:10.1155/2014/934595
20. Baek JH, Kim YS, Lee D, Huh JY, Lee JH. Benign Predominantly Solid Thyroid Nodules: Prospective Study of Efficacy of Sonographically Guided Radiofrequency Ablation Versus Control Condition. *Am J Roentgenol*. 2010;194(4):1137-1142. doi:10.2214/AJR.09.3372
21. Deandrea M, Sung JY, Limone P, et al. Efficacy and Safety of Radiofrequency Ablation Versus Observation for Nonfunctioning Benign Thyroid Nodules: A Randomized Controlled Inter-

national Collaborative Trial. *Thyroid Off J Am Thyroid Assoc*. 2015;25(8):890-896. doi:10.1089/thy.2015.0133

22. Ahn HS, Kim SJ, Park SH, Seo M. Radiofrequency ablation of benign thyroid nodules: evaluation of the treatment efficacy using ultrasonography. *Ultrasonography*. 2016;35(3):244-252. doi:10.14366/usg.15083
23. Hamidi O, Callstrom MR, Lee RA, et al. Outcomes of Radiofrequency Ablation Therapy for Large Benign Thyroid Nodules: A Mayo Clinic Case Series. *Mayo Clin Proc*. 2018;93(8):1018-1025. doi:10.1016/j.mayocp.2017.12.011
24. Che Y, Jin S, Shi C, et al. Treatment of Benign Thyroid Nodules: Comparison of Surgery with Radiofrequency Ablation. *AJNR Am J Neuroradiol*. 2015;36(7):1321-1325. doi:10.3174/ajnr.A4276
25. Hussain I, Zulfiqar F, Li X, Ahmad S, Aljammal J. Safety and Efficacy of Radiofrequency Ablation of Thyroid Nodules-Expanding Treatment Options in the United States. *J Endocr Soc*. 2021;5(8):bvab110. doi:10.1210/jendso/bvab110
26. Collins RA, McManus C, Kuo EJ, Liou R, Lee JA, Kuo JH. Improvement in thyroid-specific quality of life following radiofrequency ablation of benign thyroid nodules: A USA study. *Surgery*. 2025;177:108823. doi:10.1016/j.surg.2024.06.063
27. Spiezia S, Garberoglio R, Milone F, et al. Thyroid Nodules and Related Symptoms Are Stably Controlled Two Years After Radiofrequency Thermal Ablation. *Thyroid®*. 2009;19(3):219-225. doi:10.1089/thy.2008.0202
28. Cesareo R, Palermo A, Benvenuto D, et al. Efficacy of radiofrequency ablation in autonomous functioning thyroid nodules. A systematic review and meta-analysis. *Rev Endocr Metab Disord*. 2019;20(1):37-44. doi:10.1007/s11154-019-09487-y
29. Baek JH, Lee JH, Sung JY, et al. Complications Encountered in the Treatment of Benign Thyroid Nodules with US-guided Radiofrequency Ablation: A Multicenter Study. *Radiology*. 2012;262(1):335-342. doi:10.1148/radiol.11110416
30. Lim JY, Kuo JH. Thyroid Nodule Radiofrequency Ablation: Complications and Clinical Follow Up. *Tech Vasc Interv Radiol*. 2022;25(2). doi:10.1016/j.tvir.2022.100824
31. Chan SJ, Betcher MC, Kuo EJ, McManus CM, Lee JA, Kuo JH. Trends in thyroid function following radiofrequency ablation of benign, nonfunctioning thyroid nodules: A single institution review. Am J Surg. 2024;237:115793. doi:10.1016/j.amjsurg.2024.115793

Authors

Nina S. Li, BS, The Warren Alpert Medical School, Brown University, Providence, RI.

Sonia Giyanani, DO, The Warren Alpert Medical School, Brown University, Providence, RI.

DaeHee Kim, MD, The Warren Alpert Medical School, Brown University, Providence, RI.

Steve Kwon, MD, MPH, Boston University; Roger Williams Medical Center, Providence, RI.

John Lee, MD, The Warren Alpert Medical School, Brown University, Providence, RI.

Disclosures

None

Correspondence

John Lee, MD

JLee21@brownhealth.org

Cholangiocarcinoma in Rhode Island: Incidence Trends and Risk Profile Over the Last Decade

SASHA LIGHTFOOT, DO; SURAJ RAM, MD; ABDUL SAIED CALVINO, MD

ABSTRACT

The incidence of cholangiocarcinoma, a fatal disease of bile ducts, is increasing at unsettling rates in the Northeast United States, including Rhode Island. The cause of this region-specific increase in incidence of cholangiocarcinoma is unknown. This is a review of the literature on cholangiocarcinoma in conjunction with cancer data from the 1995–2018 Rhode Island Cancer Registry. The goal of this paper is to discuss the potential etiologies of the increased incidence in cholangiocarcinoma and identify populations in Rhode Island most at risk. Rhode Island residents have specific environmental and occupational exposures, which may contribute to the increased rate of cholangiocarcinoma. The Rhode Island Hispanic population has the highest incidence of cholangiocarcinoma and is diagnosed at younger ages. In order to evaluate and address this fatal disease, further research is needed and would be best evaluated by creation of a statewide database to track potential risk factors.

KEYWORDS: Cholangiocarcinoma; Rhode Island; disparities

INTRODUCTION

Cholangiocarcinoma, a silent and aggressive cancer of the bile ducts, casts an unsettling shadow over the United States. While it is classified as a rare malignancy, with approximately 5,000 cases diagnosed annually,[1] its incidence is not only rising but accelerating – particularly for intrahepatic cholangiocarcinoma (ICC).[2] This alarming trend is especially pronounced in Rhode Island, where the rates of this disease surpass national averages, prompting urgent questions about the underlying causes and potential risk factors that may be unique to this region.[3]

In Rhode Island, the incidence of cholangiocarcinoma is not merely a statistic; it represents a growing public health concern that affects families, communities, and healthcare systems. As we delve deeper into this issue, we find a troubling narrative: the state's historical industrial activities, particularly around the Blackstone River, have left a legacy of pollution that may be silently contributing to the rising rates of this deadly disease. The river, once celebrated as a vital artery of commerce and industry, has transformed into a symbol of environmental neglect, with its waters historically tainted by the effluents of textile mills, metalworking facilities, and other industrial operations.

Research indicates that the increase in cholangiocarcinoma cases is primarily driven by ICC, which has seen a staggering rise of 350% in incidence over the past few decades. This is striking, especially when juxtaposed with a modest increase in extrahepatic cholangiocarcinoma (ECC).[4] As we examine these trends, exploring the potential environmental and occupational exposures that may be at play becomes essential. Could the pollutants that have contaminated the Blackstone River, including industrial solvents and heavy metals, be linked to the health of Rhode Islanders?

Moreover, the prognosis for cholangiocarcinoma remains grim, with median survival rates of four to eight months.[4] Many patients remain asymptomatic until the disease has progressed significantly, complicating early detection efforts. This highlights the critical need for awareness and targeted research to identify at-risk populations in Rhode Island and understand the specific factors contributing to such high incidence rates.

This review aims to unravel the complex interplay between historical environmental exposure and the rising incidence of cholangiocarcinoma in Rhode Island. By delving into the epidemiological data, examining known risk factors, and considering the implications of industrial pollution, we seek to illuminate the path forward for research and public health interventions. As we stand at this crossroads, it is imperative to ask: what can we learn from the past, and how can we leverage this knowledge to protect future generations from the devastating impacts of cholangiocarcinoma?

UNDERSTANDING CHOLANGIOCARCINOMA

Cholangiocarcinoma is a malignancy of the bile ducts, defined based on location. ICC arises within the liver, comprising less than 10% of cholangiocarcinoma diagnoses. ECC includes cancers of the hilum, which make up 50% of cholangiocarcinoma cases, and the distal common bile duct, which makes up 40% of all cholangiocarcinoma cases. ICC and ECC are most often adenocarcinomas. Surgical resection and adjuvant chemotherapy are the preferred treatment combination for resectable tumors.[5] Cholangiocarcinoma is a fatal disease with unresectable tumors having a median

survival of less than one year. The mortality rate for cholangiocarcinoma has increased by 39%.[5] This increased mortality is related to the increased incidence of ICC.[5] ICC in the United States has increased over threefold while ECC rates have increased to a lesser extent.[3]

The incidence of cholangiocarcinoma varies based on ethnicity, gender, and region. ICC has the highest incidence in the Northeast, while ECC has the highest rates in the Northeast and Pacific regions.[6] When looking specifically at Rhode Island, the incidence of cholangiocarcinoma has more than doubled in a decade. In 1995–1999, the age-adjusted rate per 100,000 individuals was 1.10, while from 2015–2019 it was 2.18.[3] Since 1992, Rhode Island's overall cancer age-adjusted incidence has increased while the nation's cancer age-adjusted incidence has declined.[7] The questions we aim to discuss are what drives this unsettling increase in cholangiocarcinoma, and is there anything unique to the Rhode Island population contributing to this increase?

RHODE ISLAND ENVIRONMENT

The Blackstone River Valley, running from the Massachusetts border through Woonsocket, Central Falls, and Pawtucket, Rhode Island, has a long history of water pollution.[7] The river was once known as the "world's busiest river" during the 19th and 20th centuries. During this time, there was a rapid expansion of textile mills and wire, rubber, and metal factories.[8,9] Slater's Mill in Pawtucket, RI, was the nation's first textile mill, which processed cotton and dyed it.[10] Multiple dams provided hydropower for the operation of textile mills and factories.[11]

The 19th and 20th centuries were a time of rapid expansion of mills and factories employing many Rhode Islanders at the expense of the surrounding environment. Many hazardous materials in textile manufacturing involve industrial solvents that are required for printing on the textiles, weaving them, and cleaning the machinery. These chemicals, including trichloroethylene, benzene, and ethylene dichloride, were discharged directly into the Blackstone River.[12] Workers were also at risk of exposure to these chemicals as part of their occupation. Metalworking facilities produced heavy metal waste, polluting the soil and water. As industrial activity grew, human settlements proliferated along the river in the 19th century, and untreated wastewater was discharged into the river.[11]

The rapid pace of industrialization and rapid population growth through the 20th century allowed the contamination in the river from the disposal of sewage, wastewater, heavy metals, and chemical waste to reach unprecedented levels.[13] The Clean Water Act of 1972 provided water contamination standards that had to be met by 1987; however, achieving these goals in the Blackstone River has been difficult given the size and scope of the contamination. The multiple dams in the river cause contaminants to accumulate in sediment for many years.[14] By 1990, the Blackstone River had the dubious distinction of being named "America's most polluted river" by the EPA.[13]

RHODE ISLAND AND CHOLANGIOCARCINOMA

A history of occupational exposure to industrial chemicals and environmental exposure to contaminated water renders residents of Rhode Island at risk. Environmental exposure directly from polluted waters can occur with immersion or ingestion. Although there is no current evidence that drinking water quality standards are significantly breached in any significant capacity in the state, the history of pollution and occupational exposures is a risk specific to Rhode Islanders. Other studies have similarly evaluated water pollution and occupational exposure to the increasing incidence of cancers in Rhode Island. This has been thought to contribute to Rhode Island having the highest incidence of bladder cancer in the nation.[15]

Although environmental and occupational risks unique to Rhode Island may contribute to increasing the incidence of cholangiocarcinoma, there are other potential contributors to the high incidence. Males have a higher incidence of cholangiocarcinoma than females in Rhode Island, with an increase of 5.1% each year on average versus a 3.6% increase each year on average for females [**Figure 1**]. Males are more likely to be diagnosed at a younger age [**Figure 2**]. Other studies have shown that men have a higher incidence

Figure 1. Trend of Cholangiocarcinoma incidence rate from 1995 to 2018

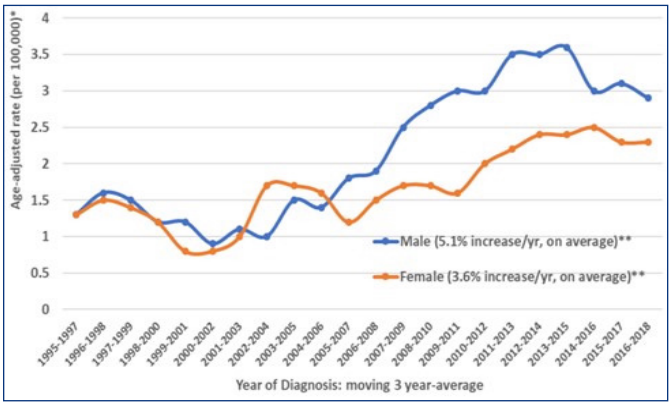


Figure 2. Age at diagnosis of Cholangiocarcinoma by sex from 1995 to 2018

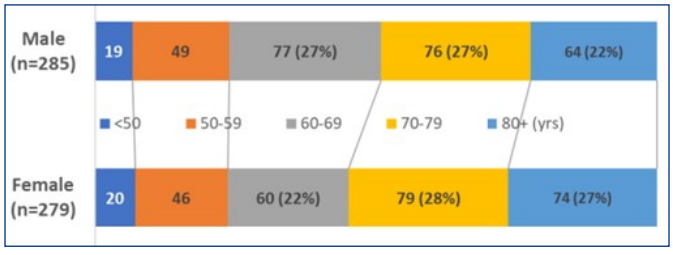


Figure 3. Incidence (rate) by sex and race/ethnicity from 1995 to 2018

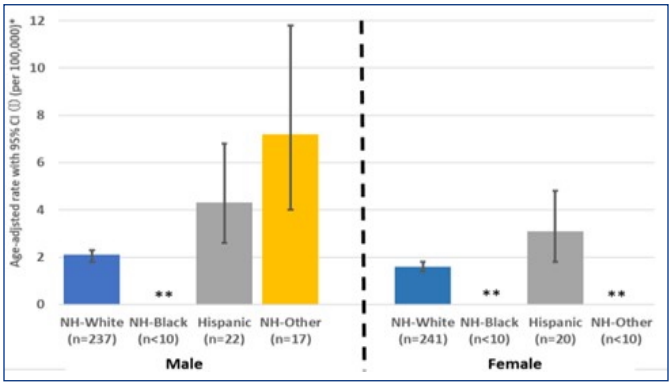
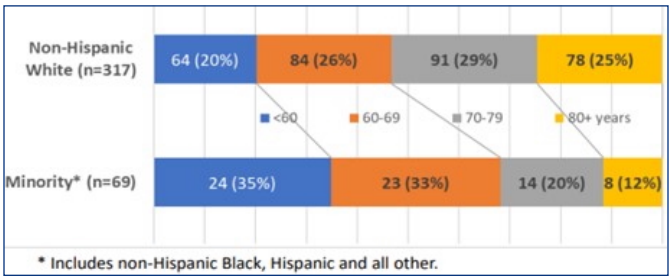


Figure 4. Age at cholangiocarcinoma diagnosis by race/ethnicity from 2007 to 2018



than women, with ratios of 1:1.2–1.5, which is in line with our data.[16,17]

In Rhode Island, age-adjusted cancer incidence rates in Hispanic people are more than double the cancer incidence rates in the non-Hispanic White population for both males and females from 1995 to 2018 [**Figure 3**]. Not only are overall cancer incidence rates higher in the Hispanic population, but incidence rates of hepatobiliary cancers, including cholangiocarcinoma, are also increasing more dramatically in the Hispanic and other minority populations in more recent years. Minority populations are also more likely to be diagnosed at younger ages [**Figure 4**]. The young age at diagnosis and the increasing incidence in the Hispanic population suggest a genetic predisposition to the diagnosis of cholangiocarcinoma.

Though genetic predisposition may contribute, the cause of increased incidence in hepatobiliary cancers in minority populations in Rhode Island is likely a multifactorial issue. Hepatitis C, HIV infection, smoking, alcohol use, and diabetes increase the risk of ICC within the United States.[1] ECC and ICC may have differing risk factors, but additional studies are needed to elucidate this further. Primary sclerosing cholangitis, choledochal cysts, and parasitic infections with the hepatobiliary flukes *Opisthorchis viverrini* and *Chlonorchis sinensis* are also associated with the diagnosis of cholangiocarcinoma. Thorotrast, a contrast agent used in the mid-1950s, is a known toxin associated with a 300-fold increase in cholangiocarcinoma.[17] To our knowledge, there is no data to determine whether these risk factors are more prevalent in the Rhode Island population than in the nation.

Social determinants of health provide another layer of complexity to the increased incidence of cholangiocarcinoma in minority populations in Rhode Island. Previous studies have demonstrated that minorities have lower education and income levels, and a lack of private insurance, which may delay their diagnosis. With delayed diagnosis, minority populations have been shown to have greater nodal involvement and higher tumor stage and are more likely to be diagnosed with metastatic disease.[18] This may be a trend seen with cholangiocarcinoma in Rhode Island minority populations as well. A study on hilar cholangiocarcinoma and treatment delay showed no impact on resectability, tumor stage, or survival, which lacks relevance to our population as this was a Danish study that did not evaluate socioeconomic determinants of health.[19-21]

More research is needed to assess the relationship between environmental pollution, occupational exposure, and genetic predisposition leading to increased cholangiocarcinomas in Rhode Island. Future studies focusing on Rhode Island residents and their proximity to the Blackstone River and occupational history are needed. This would allow us to determine if cholangiocarcinoma is higher in those with the most exposure to potential pollutants in the Blackstone River or specific occupations. Biomonitoring studies may also provide some information on past exposure to toxins and the risk of developing cholangiocarcinoma when exposed. A Rhode Island statewide database to track the incidence of cholangiocarcinoma, potential risk factors, and disparities is the next step to improve the state's outcomes in cholangiocarcinoma. The dataset would allow us to identify risk factors for the Rhode Island population and allow for directed mitigation efforts.

CONCLUSION

Cholangiocarcinoma is a highly fatal disease that uniquely impacts the Rhode Island population. This disease remains uncontrolled and unimproved in Rhode Island and nationwide due to poor comprehension of the relationship between environmental and occupational exposures, lifestyle factors, and genetic predisposition. Minorities in Rhode Island are being diagnosed at increasing rates, and national mortality rates are skyrocketing. It is time to methodically examine this disease process with continued research and efforts to improve public awareness. Policy changes are integral to mitigate environmental and occupational risks and improve access to healthcare for populations most at risk.

References

1. Shaib YH, El-Serag HB, Nooka AK, et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: a hospital-based case-control study. *Am J Gastroenterol*. May 2007;102(5):1016-21. doi:10.1111/j.1572-0241.2007.01104.x
2. Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-Year Trends in Cholangiocarcinoma Incidence in the U.S.: Intrahepatic Disease on the Rise. *Oncologist*. May 2016;21(5):594-9. doi:10.1634/theoncologist.2015-0446
3. Kidanemariam S, Gu J, Yoon JH, Challapalli JV, Fruh V, Sax AJ. Cholangiocarcinoma: Epidemiology and Imaging-Based Review. *R I Med J (2013)*. May 2 2024;107(5):43-48.
4. Mukkamalla SKR, Naseri HM, Kim BM, Katz SC, Armenio VA. Trends in Incidence and Factors Affecting Survival of Patients With Cholangiocarcinoma in the United States. *J Natl Compr Canc Netw*. Apr 2018;16(4):370-376. doi:10.6004/jnccn.2017.7056
5. Razumilava N, Gores GJ. Liver transplantation for intrahepatic cholangiocarcinoma--Authors' reply. *Lancet*. Sep 27 2014;384(9949):1182-3. doi:10.1016/S0140-6736(14)61717-7
6. Altekruse SF, Petrick JL, Rolin AI, et al. Geographic variation of intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and hepatocellular carcinoma in the United States. *PLoS One*. 2015;10(3):e0120574. doi:10.1371/journal.pone.0120574
7. Thompson J.; Fulton J. Compreshesive Cancer Control Program 2008 June; "Blackstone River Watershed 2003 Biological Assessment". Massachusetts Department of Enviromental Protection. Accessed April 14, 2025. https://www.mass.gov/files/documents/2016/08/xo/51appc.pdf
8. Kerr M. The Blackstone River. *Rhode Island Sea Grant Fact Sheet* 2003
9. Shanahan P. A water-quality history of the Blackstone River, Massachusetts, USA: Implications for Central and Eastern European Rivers. *Waster Science & Technology* 1994;30(5):59-68.
10. John H. Chafee Blackstone River Valley. National Park Service official website. Accessed March 29, 2025. https://www.nps.gov/blac/learn/historyculture/index.htm
11. Robinson K. Water Quality Trends in New England Rivers during the 20th Century. US Department of the Interior and US Geologic Survey. Accessed April 20, 2025. https://www3.epa.gov/region1/npdes/merrimackstation/pdfs/ar/AR-1255.pdf
12. Environmental Protection Agency. Textile Manufacturing. National Service Center for Environmental Publications. Accessed April 15, 2025. https://nepis.epa.gov/Exe/ZyNET.exe/10001AH6.TXT?ZyActionD=ZyDocument&Client=EPA&Index=1986+Thru+1990&Docs=&Query=&Time=&EndTime=&SearchMethod=1&TocRestrict=n&Toc=&TocEntry=&QField=&QFieldYear=&QFieldMonth=&QFieldDay=&IntQFieldOp=0&ExtQFieldOp=0&XmlQuery=&File=D%3A%5Czyfiles%5CIndex%20Data%5C86thru90%5CTxt%5C00000004%5C10001AH6.txt&User=ANONYMOUS&Password=anonymous&SortMethod=h%7C-&MaximumDocuments=1&FuzzyDegree=0&ImageQuality=r75g8/r75g8/x150y150g16/i425&Display=hpfr&DefSeekPage=x&SearchBack=ZyActionL&Back=ZyActionS&BackDesc=Results%20page&MaximumPages=1&ZyEntry=1&SeekPage=x&ZyPURL
13. National Resources Inventory and Assessment. The Blackstone River Valley National Heritage Corridor Commission. National Park Service. https://www.nps.gov/blac/learn/nature/upload/NRInv.pdf
14. Watanabe M. Is pollution causing cancer in Beluga Whales? *The Scientist magazine*. October 2, 2000
15. Faricy-Anderson KE, Fulton JP, Mega AE. Why does Rhode Island have the greatest incidence of bladder cancer in the United States? *Med Health R I*. Oct 2010;93(10):308, 313-6.
16. Khan SA, Toledano MB, Taylor-Robinson SD. Epidemiology, risk factors, and pathogenesis of cholangiocarcinoma. *HPB (Oxford)*. 2008;10(2):77-82. doi:10.1080/13651820801992641
17. Tyson GL, El-Serag HB. Risk factors for cholangiocarcinoma. *Hepatology*. Jul 2011;54(1):173-84. doi:10.1002/hep.24351
18. Shulman RM, Deng M, Handorf EA, Meyer JE, Lynch SM, Arora S. Factors Associated With Racial and Ethnic Disparities in Locally Advanced Rectal Cancer Outcomes. *JAMA Netw Open*. Feb 5 2024;7(2):e240044. doi:10.1001/jamanetworkopen.2024.0044
19. Ruys AT, Groot Koerkamp B, Wiggers JK, Klumpen HJ, ten Kate FJ, van Gulik TM. Prognostic biomarkers in patients with resected cholangiocarcinoma: a systematic review and meta-analysis. *Ann Surg Oncol*. Feb 2014;21(2):487-500. doi:10.1245/s10434-013-3286-x
20. Ruys AT, Heuts SG, Rauws EA, Busch OR, Gouma DJ, van Gulik TM. Delay in surgical treatment of patients with hilar cholangiocarcinoma: does time impact outcomes? *HPB (Oxford)*. May 2014;16(5):469-74. doi:10.1111/hpb.12156
21. Ruys AT, van Haelst S, Busch OR, Rauws EA, Gouma DJ, van Gulik TM. Long-term survival in hilar cholangiocarcinoma also possible in unresectable patients. *World J Surg*. Sep 2012;36(9):2179-86. doi:10.1007/s00268-012-1638-5

Authors

Sasha Lightfoot, DO, Boston University; Roger Williams Medical Center, Providence, RI.

Suraj Ram, MD, Boston University; Roger Williams Medical Center, Providence, RI.

Abdul Saied Calvino, MD, Boston University; Roger Williams Medical Center, Providence, RI.

Disclosures

None of the contributing authors have disclosures.

Correspondence

Abdul Saied Calvino, MD

abdul.saied@chartercare.org

FREE TO FOCUS ON KARLY.

With healthcare's constant complexities and distractions, it can be difficult to focus on patients. We can help, with proven medical professional liability insurance and so much more. So you are free to focus on delivering superior patient care.

- Medical Professional Liability Insurance
- Claims Analytics
- Risk Mitigation
- Medicare Contractual Risk Protection
- And more

coverys.com 800.225.6168

COVERYS FREE TO FOCUS℠

Crusted Lesion on Left Maxilla After Mohs Surgery

ALYSSA M. IURILLO, BA; VICTORIA J. SHI, BA; TATIANA ABRANTES, MD; OLIVER J. WISCO, DO

A 53-year old female with a history of basal cell carcinoma (BCC) presented with a crusted, brown plaque overlying a linear surgical scar on the left maxilla. Approximately two months prior to presentation, the patient underwent Mohs micrographic surgery for removal of a biopsy-proven nodular BCC of the left maxilla. Preoperatively, the lesion presented as a 0.8 cm crusted pink papule [**Figure 1**]. The BCC was removed in two stages and the defect was approximated with a complex linear closure. Three days postoperatively, the patient developed a surgical site infection, which resolved with a 10-day course of doxycycline 100mg taken twice daily.

At the current visit, physical examination revealed a hyperkeratotic, tan to brown plaque in a linear distribution on the left cheek extending towards the ear (**Figure 2**). The patient reported cleaning the area with soap and water several times per day and applying Vaseline over the site without improvement. There was no pain or drainage. In the office, the hyperkeratotic plaque was loosened and removed by wiping with a hydrogen peroxide-soaked pad. Removal of the brown hyperkeratosis revealed a well-healed surgical scar with faint erythema on the left cheek (**Figure 3).** This case represents an example of Terra Firma-Forme Dermatosis (TFFD), a benign condition characterized by retained keratin that can be removed with alcohol or hydrogen peroxide.

TFFD is an idiopathic, benign skin condition caused by abnormal keratinocyte retention and characterized by hyperpigmented dirtlike plaques that are resistant to usual cleansing methods (i.e., soap and water) but clear with rubbing alcohol.[1,2] As with the patient in this case, patients with TFFD often report appropriate hygiene and robust, yet unsuccessful attempts at cleansing the affected area. The alcohol swab test is a simple method of promptly resolving skin lesions, confirming the diagnosis and should be attempted before other more invasive investigations.[1] Further testing including laboratory testing or skin biopsy is typically not necessary; however, fungal culture may be obtained to rule out pityriasis versicolor. TFFD is most prevalent in children, has no gender or familial predisposition and has been reported in all ethnic groups.[3-5]

Classic TFFD, as depicted in this case, is characterized by brown to gray to black macules and patches depicting a "dirt-like" appearance. The lesions often have a smooth, velvety, or scaly texture with fine scale when palpated, and can remain unnoticed due to its asymptomatic nature. Additional types include verrucous, papillomatous, and reticular patterns with islands of spared normal skin between the

Figure 1. 0.8 cm crusted pink papule on left maxilla.

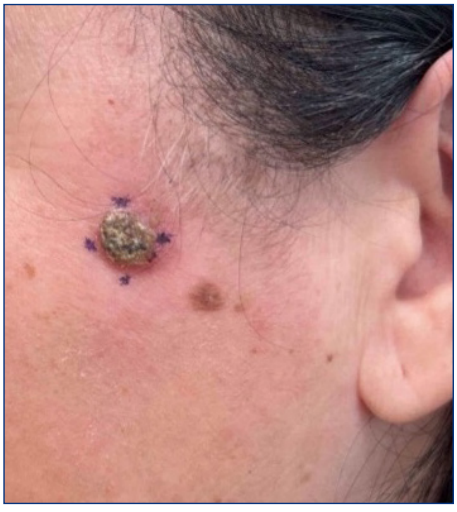


Figure 2. Hyperkeratotic, tan to brown plaque in a linear distribution on the left cheek extending towards the ear.

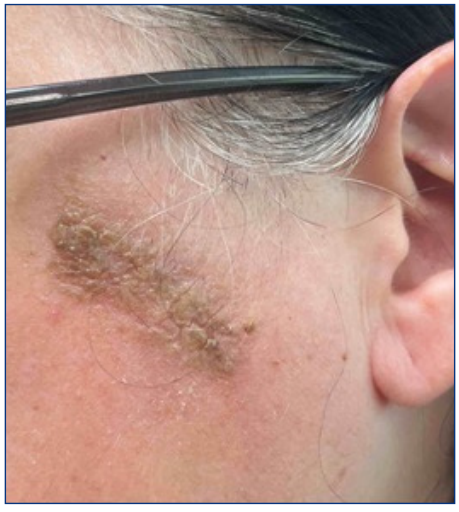
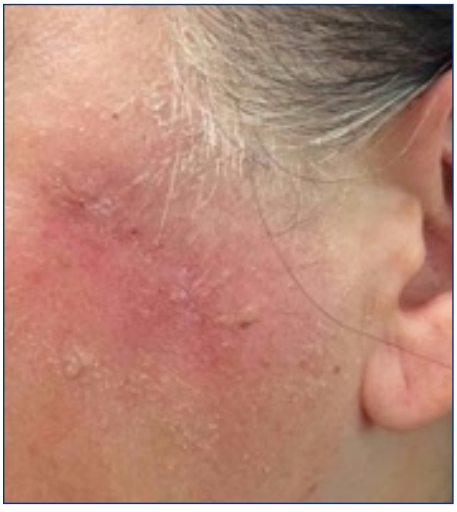


Figure 3. Surgical scar with faint erythema on the left cheek.



lesions.[6] TTFD commonly involves the face, neck, trunk, navel, ankle, and concave contours of the body.[7] The dermoscopic characteristics of TFFD present as "polygonal, plate-like brown scales organized in a distinctive mosaic pattern."[8]

Dermatosis neglecta is characterized by hyperpigmented, adherent, cornflake-like scales that can be removed with soap and water, unlike TFFD, which requires alcohol for removal.[7] Pityriasis versicolor is a fungal infection that causes well-demarcated, often scaly patches that can be white, pink, or brown, but doesn't typically produce the thick, crusted plaques seen in TFFD.[7] Seborrheic keratoses (SK) typically present as an exophytic lesion with a well-defined border, giving it a characteristic "stuck-on" appearance. The sharply demarcated appearance of SK distinguishes it from conditions like TFFD, as SK is a true epidermal lesion with a thickened surface that cannot be easily wiped off.[9]

TFFD is a noninfectious dermatosis that resolves with alcohol or hydrogen peroxide, distinguishing it from dermatosis neglecta, pityriasis versicolor, and seborrheic keratosis. This case highlights the importance of recognizing TFFD to avoid unnecessary interventions, as its diagnosis is readily confirmed with the alcohol swab test and does not require biopsy or laboratory testing.

References

1. Greywal T, Cohen PR. Terra firma-forme dermatosis: A report of ten individuals with Duncan's dirty dermatosis and literature review. Dermatol Pract Concept. 2015 Jul 31;5(3):29-33. doi: 10.5826/dpc.0503a08. PMID: 26336622; PMCID: PMC4536880.
2. Aslan NÇ, Güler Ş, Demirci K, Isiyel E. Features of Terra Firma-Forme Dermatosis. Ann Fam Med. 2018 Jan;16(1):52-54. doi: 10.1370/afm.2175. PMID: 29311175; PMCID: PMC5758320.
3. Mattessich S, Aubert P, Rees A. Bilateral brown plaques behind the ears. Cutis. 2018;102:E1–3.
4. Özuğuz P, Kaçar SD, Kurtipek GS, Tunçez AF. The early onset case of terra firma forme dermatosis. Tıp AraştırmalarıDergisi. 2015;13:137–9.
5. Pallure V, Ameline M, Plantin P, Bessis D. Terra firma-forme dermatosis. Ann Dermatol Venereol. 2013;140:693–8.
6. Sechi A, Patrizi A, Savoia F, Neri I. Terra firma-forme dermatosis. Clin Dermatol. 2021;39:202–5.
7. Mohta A, Sarkar R, Narayan RV, Deoghare S, Arora A. Terra Firma-Forme Dermatosis-More Than Just Dirty. Indian Dermatol Online J. 2023 Dec 22;15(1):99-104. doi: 10.4103/idoj.idoj_424_23. PMID: 38283007; PMCID: PMC10810366.
8. Vakirlis E, Theodosiou G, Lallas A, Apalla Z, Sotiriou E. Terra firma-forme dermatosis: Differential diagnosis and response to salicylic acid therapy. Pediatr Dermatol. 2019 Jul;36(4):501-504. doi: 10.1111/pde.13807. Epub 2019 Mar 24. PMID: 30907017.
9. Barthelmann S, Butsch F, Lang BM, Stege H, Großmann B, Schepler H, Grabbe S. Seborrheic keratosis. J Dtsch Dermatol Ges. 2023 Mar;21(3):265-277. doi: 10.1111/ddg.14984. Epub 2023 Mar 9. PMID: 36892019.

Authors

Alyssa M. Iurillo, BA, Indiana University School of Medicine, Indianapolis, IN.

Victoria J. Shi, BA, University of Missouri-Kansas City School of Medicine, Kansas City, MO.

Tatiana Abrantes, MD, Department of Dermatology, The Warren Alpert Medical School of Brown University, Providence, RI.

Oliver J. Wisco, DO, Department of Dermatology, The Warren Alpert Medical School of Brown University, Providence, RI.

Disclosures

None

Correspondence

Alyssa Iurillo, BA
340 W 10th St
Indianapolis, IN 46202
317-274-8157
Fax 317-278-5241
aiurillo@iu.edu

Comparing Sports-Related Orthopedic Injury Trends on Artificial Turf and Natural Grass: A 20-Year Nationwide Analysis of the NEISS Database

TIMOTHY A. REIAD, BS; JOHN D. MILNER, MD; PETER V. DINH, BS; JOHN PIETRO, BS; RIGEL P. HALL, BS; JONATHAN LIU, MD; BRETT D. OWENS, MD; STEPHEN E. MARCACCIO, MD

ABSTRACT

OBJECTIVES: The impact of playing surfaces on sports-related injuries remains a subject of debate, with limited research comparing injury patterns across various sports and competition levels.

METHODS: This study utilized the National Electronic Injury Surveillance System (NEISS) database from 2004 to 2023. Sports-related injuries that occurred on artificial turf and natural grass playing surfaces were identified and analyzed.

RESULTS: Of 21,868 injuries, 76.3% occurred on grass and 23.7% on turf. Rugby (OR: 8.35) and lacrosse (OR: 8.42) injuries were more common on turf, while soccer and softball injuries were more frequent on grass. Dislocations (OR: 4.73) and lacerations (OR: 5.41) were more likely on grass, while strains/sprains (OR: 1.16) and contusions (OR: 1.96) were more common on turf.

CONCLUSION: This study reveals significant variations in injury patterns that occur on artificial turf and natural grass playing surfaces across various sports and age, providing valuable evidence on the potential risks and differences in injury patterns associated with each surface.

KEYWORDS: sports medicine; turf; grass; injury epidemiology; playing surfaces; sports injury

INTRODUCTION

In the United States, over 8.5 million individuals participate in high school and collegiate athletics each year, with an additional 10,000–15,000 athletes competing at the professional level.[1,2] Prior literature has estimated that 90% of high school athletes suffer at least one injury during their playing career, with 30–40% suffering multiple injuries.[3] The prevalence of injuries is particularly high in contact sports, affecting 75–80% of high school and 66–75% of collegiate athletes.[2-4] Given the high incidence of injuries among athletes, the identification of risk factors for injury and the implementation of appropriate prevention strategies is crucial. One recent area of focus has been the impact of playing surfaces on injury rates, particularly the comparison between natural grass and artificial turf. Despite these concerns, definitive conclusions about the injury risks of artificial turf remain unclear due to heterogeneity in study design and inconsistent findings regarding injury epidemiology across surfaces.[5-12]

While sports have traditionally been played on natural grass, artificial turf, first introduced in the 1960s, has gained popularity as an alternative to grass playing surfaces due to its lower maintenance costs and long-term durability. Current literature states that artificial turf systems are less compliant and thus stiffer than grass counterparts, leading to an overall decrease in shock absorption.[13] This decreased shock absorption is thought to inflict a greater rebound force on athletes leading to greater injury risk; however, the validity of this claim is debated and this effect may vary greatly with the type of turf used.[13]

Prior studies regarding the epidemiology of injuries sustained on artificial turf and natural grass surfaces have demonstrated variable results, depending on factors such as sport type, level of competition, artificial turf subtype, and whether an athlete is practicing or competing in a game.[14–22] As the use of artificial surfaces continues to increase, understanding the impact of these playing surfaces on athlete health is pivotal to addressing the high injury rates among athletes and between different sports. Therefore, our limited understanding of the impact of playing surfaces on athlete injury warrants further investigation.

The current study conducts a population-level analysis to compare sports-related injury rates on artificial turf and natural grass surfaces, seeking to provide a comprehensive breakdown of specific risk factors and injury patterns that may inform injury prevention strategies. We hypothesize that the distribution of injury location and injury type will differ considerably between the two playing surfaces. These findings will provide valuable information for athletic programs considering surface transitions and enable the implementation of targeted preventative measures.

MATERIALS AND METHODS

Data Collection

This retrospective cross-sectional analysis utilized data from the US Consumer Product Safety Commission's (CPSC) National Electronic Injury Surveillance System (NEISS) over a 20-year study period from 2004 to 2023.[23] The NEISS database compiles data from a nationally representative

sample of 100 hospital emergency departments. Each case includes pertinent patient- and encounter-level details from emergency departments. The NEISS database has been consistently used in several prior nationally representative orthopedic studies as a reliable source for analyzing injury epidemiology.[24-31]

Over the 20-year study period, the NEISS recorded 7,306,740 cases, representing a total of 269,671,422 nationally estimated cases. To isolate the relevant cases, injuries occurring in a place of recreation or sports (NEISS location code = 9) and injuries occurring specifically while playing a sport, as specified by the sport activity codes provided by the NEISS coding manual were isolated, leaving a total of N =19,835,980 sport-related cases.[32] To focus on orthopedic injuries, we excluded cases where the injured body part was the eyeball, head, mouth, face, ear, internal organs, pubic region, or other non-specific areas, leaving a total of N = 15,690,498 cases for investigation. The "Narrative" cases for this isolated group were then queried for "turf" or "grass." Cases where the narrative mentioned "turf" but not "grass" were considered "turf" cases. Cases where the narrative mentioned "grass" but not "turf" were considered "grass" cases. Narratives that mentioned both or neither were excluded. Remaining narratives were manually reviewed to ensure that the remaining cases included an accurate and relevant sport-related, turf-or-grass-related, orthopedic injury. This left us with N = 681 cases, representing a nationally estimated N = 21,868 cases, comprising N = 5,184 injuries occurring on turf and 16,684 injuries occurring on grass.

Data for each case include variables such as treatment date, patient age, sex, race, diagnosis, injured body part, patient outcome, place of injury, and two narrative descriptions. Age was categorized into the following groups: under 5, 5–14, 15–24, 25–44, 45–64, 65 and older. Injury data were categorized according to NEISS's coding system, which assigns to each case a diagnosis and injured body region. For example, a shoulder dislocation while playing rugby would be coded as: body part = 30 (shoulder); diagnosis = 55 (dislocation); activity/product code = 3234 (rugby). The NEISS does not use ICD-9 or ICD-10 diagnostic codes. Instead, it utilizes a proprietary coding system to categorize diagnosis types and body parts affected, allowing for standardized national surveillance and injury mechanism analysis.[32] Diagnoses included strain/sprain, contusion/abrasion, laceration/puncture, dislocation, fracture, burn, and "other." The NEISS dataset uses broad categories to describe the anatomical locations of fractures, which may encompass more specific fracture sites. For the upper extremity, fractures in the lower arm may involve the radius or ulna in the forearm. In the upper arm, the humerus may be fractured at the proximal, shaft, or distal sections. Elbow fractures can affect the distal humerus, proximal ulna, or proximal radius, including the olecranon or radial head. Finger fractures may involve the phalanges (proximal, middle, or distal) of specific digits, while hand fractures often involve the metacarpal bones. Neck fractures may involve the cervical vertebrae, whereas shoulder fractures may affect the clavicle, scapula, or proximal humerus. Wrist fractures may involve the distal radius, distal ulna, or carpal bones. For the lower extremities, ankle fractures may involve the distal tibia, distal fibula, or talus. Foot fractures may affect the tarsals, metatarsals, or phalanges. Knee fractures may involve the patella, distal femur, or proximal tibia, while lower leg fractures can affect the tibia or fibula, either in the shaft or distal ends. Upper leg fractures may involve the femur, specifically the proximal femur (hip), femoral shaft, or distal femur near the knee. Toe fractures may affect the phalanges (proximal, middle, or distal) of specific digits. For the trunk, fractures in the lower trunk may involve the lumbar spine, sacrum, coccyx, pelvis, or nearby bones. Upper trunk fractures may affect the thoracic spine, clavicle, scapula, ribs, or adjacent structures.

Statistical Analysis

Student's *t*-test and *chi*-square analyses were used to compare demographics between the artificial turf and natural grass cohorts. For each comparison, odds ratios and their respective 95% confidence interval (CI) were utilized to compare the likelihood of specific events occurring on turf versus grass. All statistical analyses were performed using Stata Statistical Software 18.0 (College Station, TX: StataCorp LLC). Following CPSC guidelines, statistical analyses, and tests were performed using weighted sampling techniques applied to the injuries, with the Survey Estimation Module in Stata used to account for the survey design of the NEISS database, including sampling strata and clustering variables. A p-value of <0.05 was determined to represent statistical significance.

RESULTS

A total of 21,868 sports-related injuries were identified with 16,684 (76.3%) injuries occurring on natural grass and 5,184 (23.7%) injuries occurring on artificial turf [**Table 1**]. There were no statistically significant differences in age or sex between the natural grass and artificial turf cohorts. The average age of athletes with injuries occurring on natural grass was 25.4 years old compared to 21.4 years old for athletes injured on artificial turf. This age difference was not statistically significant (p = 0.41). Both groups were predominantly male with 73.9% of athletes being male in the natural grass group and 82.2% males in the artificial turf group. The identified injuries were primarily sustained by white athletes (46.7%); a full demographic breakdown is provided in **Table 1** and **Figure 1**.

Injuries on artificial turf playing surfaces were most prevalent in football (53.2% of injuries) followed by soccer (29.8%) and rugby (4.9%) [**Table 2**]. When compared to injury rates on grass, rugby and lacrosse injuries were 8.35

and 8.42 times more likely on turf (p <0.01), respectively, whereas football injuries were 2.49 times more likely on turf (p <0.01). Injuries sustained on natural grass playing surfaces were most prevalent among soccer (35.4%), football (31.1%), and softball (7.7%) players. Compared to injury rates on turf surfaces, there was a higher injury rate on grass among athletes playing softball and soccer (p = 0.012).

Table 1. Demographics and Descriptive Statistics

	Grass	Turf
Total N = 21,868	N = 16,684 (76.29%)	N = 5,184 (23.71%)
Mean Age	25.41	21.37
Sex	N (%*)	N (%*)
Female	4,347 (26.06)	924 (17.83)
Male	12,337 (73.94)	4,260 (82.17)
Race		
White	8,248 (49.44)	1,968 (37.97)
Black/African American	1,337 (8.02)	713 (13.74)
Asian	204 (1.22)	20 (0.38)
American Indian/ Alaska Native	74 (0.45)	55 (1.06)
Not stated	2,009 (12.04)	525 (10.13)
Other	4,810 (28.83)	1,904 (36.72)

*Represents the column percentage of either total turf or total grass injuries.

Figure 1A. Age distribution of injuries: Turf

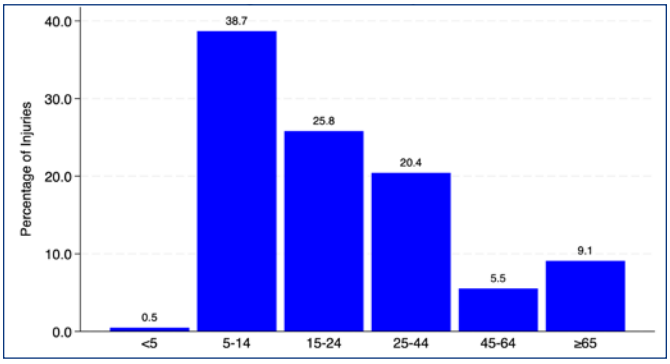


Figure 1B. Age distribution of injuries: Grass

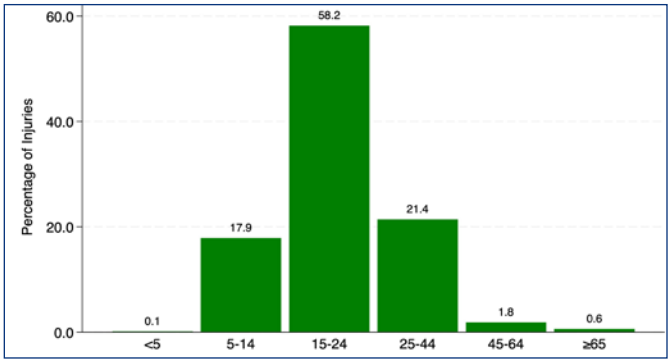


Table 2. Distribution of Athletic Injuries on Grass vs. Turf by Sport with Odds Ratio (OR)

Sport	Turf N (%*)	OR on Turf (95% CI, p-value)	Grass N (%*)	OR on Grass (95% CI, p-value)
Football	2,758 (53.19)	2.49 (2.35–2.62, p <0.01)	5,234 (31.37)	—
Soccer	1,542 (29.75)	—	5,887 (35.28)	1.29 (1.25–1.33, p <0.01)
Softball	356 (6.86)	—	1,253 (7.51)	1.1 (1.04–1.17, *p* = 0.012)
Rugby	251 (4.85)	8.35 (7.33–9.49, p <0.01)	101(0.60)	—
Lacrosse	180 (3.47)	8.42 (7.21–9.77, p <0.01)	71 (0.43)	—
Distribution of Athletic Injuries on Grass vs. Turf by Diagnosis with Odds Ratios (OR)				
Laceration	79 (1.53)	—	1,288 (7.72)	5.41 (5.10–5.72, p <0.01)
Dislocation	73 (1.40)	—	980 (5.87)	4.73 (4.09–4.66, p <0.01)
Fracture	1,109 (21.39)	—	4,717 (28.27)	1.45 (1.40–1.50, p <0.01)
Contusions/Abrasions	1,039 (20.04)	1.96 (1.83–2.10, p <0.01)	1,893 (11.34)	—
Strain/Sprain	1,795 (34.61)	1.16 (1.09–1.23, p <0.01)	5,232 (31.36)	—
Distribution of Athletic Injuries on Grass vs. Turf by Body Part with Odds Ratios (OR)				
Toe	554 (10.69%)	6.30 (5.76–6.88, p <0.01)	311 (1.87%)	—
Hand	189 (3.64%)	6.15 (5.28–7.11, p <0.01)	102 (0.61%)	—
Upper Leg	140 (2.69%)	2.05 (1.72–2.43, p <0.01)	223 (1.34%)	—
Foot	447 (8.62%)	1.67 (1.51–1.84, p <0.01)	894 (5.36%)	—
Lower Leg (excluding knee/ankle)	571 (11.01%)	1.59 (1.46–1.74, p <0.01)	1,203 (7.21%)	—
Elbow	448 (8.63%)	1.36 (1.23–1.50, p <0.01)	1,082 (6.49%)	—
Upper Trunk (excluding shoulder)	32 (0.62%)	—	895 (5.37%)	9.13 (8.52–9.76, p <0.01)
Lower Arm (excluding elbow/wrist)	81 (1.56%)	—	1,221 (7.32%)	4.90 (3.69–5.27, p <0.01)
Wrist	106 (2.04%)	—	973 (5.83%)	2.97 (2.78–3.17, p <0.01)
Ankle	481 (9.27%)	—	2,737 (16.41%)	1.92 (1.84–2.00, p <0.01)

Table 3. Odds Ratios (OR) by *Body Part and Diagnosis* on Turf vs. Grass

Body Part	Diagnosis	Grass (%*)	Turf (%*)	OR on Turf (95% CI, p-value)	OR on Grass (95% CI, p-value)
Lower Leg (excluding knee or ankle)	Contusion/Abrasion	1.99	98.01	56.04 (38.50–84.63, p <0.01)	—
Hand	Fracture	9.83	90.17	9.4 (7.71–11.73, p <0.01)	—
Foot	Strain/Sprain	19.32	80.68	4.36 (3.87–4.89, p <0.01)	—
Elbow	Fracture	26.36	73.64	2.85 (2.33–3.50, p <0.01)	—
Wrist	Fracture	88.99	11.01	—	8.16 (7.46–8.11, p <0.01)
Knee	Dislocation	86.02	13.98	—	6.36 (5.74–7.02, p <0.01)
Lower Trunk	Strain/Sprain	87.34	12.66	—	7.04 (6.30–7.85, p <0.01)
Upper Trunk (excluding shoulder)	Contusion/Abrasion	85.78	14.22	—	6.16 (5.49–6.89, p <0.01)
Shoulder (including clavicle)	Dislocation	82.63	17.37	—	4.82 (4.21–5.49, p <0.01)
Elbow	Strain/Sprain	79.43	20.57	—	3.91 (3.36–4.51, p <0.01)
Lower Leg (excluding knee or ankle)	Fracture	75.00	25.00	—	3.09 (2.75–3.47, p <0.01)
Lower Arm (excluding elbow or wrist)	Fracture	73.49	26.51	—	2.83 (2.61–3.08, p <0.01)
Ankle	Fracture	71.09	28.91	—	2.55 (2.37–2.74, p <0.01)
Foot	Fracture	71.30	28.70	—	2.53 (2.38–2.80, p <0.01)

*Represents the row percentage of either total turf or total grass injuries.

Table 4. Odds Ratios (OR) by *Body Part, Diagnosis, and Sport* on Turf vs. Grass

Body Part	Diagnosis	Sport	Grass (%*)	Turf (%*)	OR on Turf (95% CI, p-value)	OR on Grass (95% CI, p-value)
Knee	Dislocation	Soccer	8.06	91.94	10.77 (6.57–16.64, p <0.01)	—
Elbow	Fracture	Football	23.18	76.82	13.53 (10.87–16.65, p <0.01)	—
Elbow	Contusion/ Abrasion	Football	6.96	93.04	13.39 (10.63–17.3, p <0.01)	—
Shoulder (including clavicle)	Fracture	Football	8.38	91.62	11.10 (9.31–13.15, p <0.01)	—
Shoulder (including clavicle)	Dislocation	Soccer	9.18	90.82	9.68 (5.41–15.98, p <0.01)	—
Toe	Fracture	Soccer	9.48	90.52	9.68 (5.41–15.98, p <0.01)	—
Foot	Strain/Sprain	Soccer	14.62	85.38	6.01 (5.08–7.06, p <0.01)	—
Lower Leg (excluding knee or ankle)	Strain/Sprain	Soccer	23.50	76.50	3.31 (2.25–4.70, p <0.01)	—
Lower Arm (excluding elbow or wrist)	Fracture	Soccer	95.82	4.18	—	22.24 (20.13–24.50, p <0.01)
Wrist	Fracture	Soccer	90.36	9.64	—	9.38 (8.51–10.31, p <0.01)
Shoulder (including clavicle)	Fracture	Soccer	81.82	18.18	—	4.50 (4.00–5.05, p <0.01)
Lower Leg (excluding knee or ankle)	Fracture	Football	75.88	24.12	—	3.09 (2.54–3.73, p <0.01)

*Represents the row percentage of either total turf or total grass injuries

When looking at the prevalence of specific types of injuries that occurred on grass versus turf, we found that dislocations, lacerations, fractures, and ankle injuries were more likely to occur on grass playing surfaces [**Table 2**], whereas contusions/abrasions, strains/sprains, and burns were more likely to occur on turf surfaces [**Table 2**]. Dislocations were 4.73 times more likely on grass than on turf (p <0.01). Lacerations were 5.41 times more likely on grass than on turf (p <0.01). Fractures were 1.45 times more likely on grass than on turf (p <0.01).

When looking at specific body parts injured on grass versus turf, we found that toe, elbow, hand, upper leg, lower leg, and foot injuries were more likely to occur on turf, whereas upper trunk, forearm, wrist, and ankle injuries were more likely to occur on grass [**Table 2**]. Toe injuries were 6.30 times more likely on turf than on grass (p <0.01). Elbow injuries were 1.36 times more likely to occur on turf than grass (p <0.01). Hand injuries were 6.15 times more likely on turf than on grass (p <0.01). Upper leg injuries were 2.05 times more likely on turf than on grass (p <0.01). Lower leg injuries were 1.59 times more likely on turf than on grass (p <0.01). Foot injuries were 1.67 times more likely on turf than on grass (p <0.01). However, on grass playing surfaces, upper trunk injuries were 9.13 times more likely. Forearm injuries were 4.9 times more likely on grass than on turf (p <0.01). Wrist injuries were 2.97 times more likely on grass

than on turf (p <0.01). Finally, ankle injuries were 1.92 times more likely on grass than on turf (p <0.01).

When looking at both common diagnoses and the specific anatomical location injured across all sports, we found that lower leg contusions, elbow and hand fractures, and foot strain/sprains were more likely on turf while forearm fractures, wrist fractures, knee dislocations, lower trunk strain/sprain, upper trunk contusion, shoulder dislocations, elbow strain/sprain, lower leg fractures, and ankle/foot fractures were more likely on grass than turf [**Table 3**]. Lower leg contusions/abrasions were 56.04 times more likely on turf (p <0.01). Elbow fractures were 2.85 times more likely on turf (p <0.01). Hand fractures were 9.4 times more likely to occur on turf (p <0.01). Foot strain/sprains were 4.36 times more likely on turf (p <0.01). Conversely, forearm and wrist fractures were 2.83 and 8.16 times more likely on grass, respectively (p <0.01). Knee dislocations were 6.36 times more likely on grass (p <0.01), whereas ankle fractures were 2.55 times more likely on grass (p <0.01). Foot fractures were 2.53 times more likely on grass (p <0.01). Lower trunk strain/sprains were 7.04 times more likely on grass (p <0.01). Upper trunk contusions were 6.16 times more likely on grass (p <0.01). Elbow strain/sprains were 3.91 times more likely on grass (p <0.01). Lower leg fractures were 3.09 times more likely on grass (p <0.01).

DISCUSSION

Artificial turf is widely used as an alternative playing surface to natural grass for all levels of athletic competition and offers improved cost, durability, and maintenance requirements.[33] However, concerns persist regarding its safety, particularly among professional athletes. Within the National Football League (NFL), for instance, players have expressed notable apprehension about the injury risks associated with artificial surfaces; these concerns have been substantiated by recent studies linking artificial turf to higher injury rates within the NFL.[34,35] Biomechanical studies also suggest artificial turf generates greater torque and rotational stiffness compared to natural grass, potentially increasing injury risk.[36-38]

These significant differences between playing surfaces suggest that biomechanical interactions between athletes and playing surfaces are complex and sport dependent. Biomechanical studies suggest artificial turf exhibits increased torque, rotational stiffness, decreased force absorption, and less cleat release than natural grass.[36-38] This increased "grip" may lead to greater forces being transmitted to an athlete's lower extremities during rapid changes in direction or when the foot becomes fixed to the surface. These factors likely contribute to the increased rate of lower extremity injuries observed on turf in this study. Additionally, the elevated surface temperatures, harder composition, and abrasive texture of artificial turf may explain the increased likelihood of contusions and abrasions and the exclusive observation of burns on this surface in the present study.[33,39]

In contrast, natural grass provides greater force absorption and cleat release under stress, potentially reducing some injury risks. Surface variability and maintenance-related inconsistencies may explain the increased prevalence of dislocations, lacerations, and fractures observed in this study.[33,35]

The observed differences in injury patterns between artificial turf and natural grass across various sports highlight the complex interplay between playing surface characteristics and sport-specific biomechanics. Injuries in football, rugby, and lacrosse were more likely on turf playing surfaces, whereas injuries in soccer (p <0.01) and softball (p = 0.012) were more likely on natural grass. For instance, the higher risk of knee dislocations in soccer players on artificial turf may be related to the sport's emphasis on rapid cutting movements and sudden stops, which could be exacerbated by the surface's higher friction. In contrast, the increased likelihood of shoulder and elbow fractures in football players on turf might be due to the harder surface leading to greater impact forces during tackles and falls. The characteristic hardness and reduced energy absorption of turf compared to natural grass supports a 96% higher contusion risk on artificial turf compared to grass. This biomechanical difference likely increases impact forces during ball-player collisions because it enables lacrosse balls and softballs to maintain greater post-bounce velocities. The surface-ball interaction hypothesis is supported by sport-specific injury patterns. Lacrosse injuries were 8.42 times more likely on turf, concentrated in upper extremity regions, suggesting faster-moving balls increase defensive reaction errors and impact severity.

Artificial turf's high energy return in comparison to grass surfaces facilitates faster movements but may inadvertently increase high-speed collision potential.[40] Turf-associated upper leg injuries (OR 2.05) and lower leg contusions (OR 56.04) could reflect both direct surface contact injuries and increased collision forces. However, this effect appears sport-dependent, as evidenced by soccer's grass-dominated injury pattern.

These results can inform preventive measures to reduce the rate of injury and provide valuable information for programs considering the benefits and risks of natural grass and turf playing surfaces. The higher incidence of contusions, abrasions, and burns on turf surfaces necessitates improved and directed protective measures, including appropriate clothing and equipment. For grass surfaces, interventions should focus on mitigating factors contributing to dislocations and fractures. This may include optimizing field maintenance practices where financially feasible, implementing player training programs to enhance balance and landing mechanics, exploring cleat designs that balance traction with joint protection, and educating athletes about surface-specific risks.

Strength and conditioning programs should also adapt to the primary playing surface, emphasizing upper-body strength and fall techniques for turf, and lower-body

stability for grass. Equipment manufacturers can contribute by developing specialized protective gear, such as reinforced upper body padding for turf play and specialized cleats for grass surfaces. Similarly, sports medicine teams must be prepared for the distinct injury profiles of each surface, ensuring appropriate on–field and follow–up care. Educating athletes, coaches, and parents about these differential risks is essential for promoting proactive injury prevention across all levels of play.

Limitations

Our study has several limitations that warrant consideration. The main limitation involves the structure and specificity of the NEISS database. The coding system does not allow for granular anatomical or diagnostic specificity. For example, common injuries in athletic populations, such as hamstring strains and tears would be grouped broadly under "upper leg" (body part code = 81) and "strain/sprain" (diagnosis code = 64). This limits our ability to identify specific muscle injuries or detailed injury patterns. Similarly, broad, nonspecific categories like "upper trunk" or "lower trunk" include a wide range of potential body parts and injuries. These factors may reduce clinical specificity. Moreover, while NEISS data are coded by trained professionals at participating hospitals using standardized criteria, variability in chart interpretation and reporting may introduce inconsistency. Coding accuracy relies on both the detail of clinician documentation and the coders' interpretation of that information, which may result in some degree of misclassification or generalization of an injury or diagnosis.

Additionally, the retrospective design limits causal inferences about the relationship between surface type and injury risk. The majority of injuries (76.29%) were found to have occurred on grass, with only 23.71% on turf, however, it is most likely that far more games and practices were held on natural grass, so this may not necessarily reflect the differences in relative safety. Data collection from emergency room records may have skewed the results towards more severe injuries, as minor injuries are less likely to require emergency care. Additionally, reliance on narrative data to identify surface type may have introduced misclassification bias. The lack of exposure data (e.g., time spent playing on each surface) limits the ability to calculate true injury rates. Lastly, confounding factors such as shoe type, rest time, field conditions, generation of artificial turf, field maintenance conditions, previous injury history, and level of competition were unable to be controlled for.

CONCLUSION

In conclusion, this study reveals significant variations in injury patterns that occur on artificial turf and natural grass playing surfaces across various sports and age, providing valuable evidence on the potential risks and injury patterns associated with each surface. These findings can inform tailored interventions, equipment standards, and athlete education to improve player safety. Further research is needed to investigate biomechanical mechanisms underlying surface-specific risks and to develop comprehensive prevention strategies that address demographic and environmental factors.

References

1. NCAA Sports Sponsorship and Participation Rates Report. NCAA Sports Sponsorship and Participation. September 29, 2023. Accessed October 9, 2024. https://ncaaorg.s3.amazonaws.com/research/sportpart/2023RES_SportsSponsorshipParticipationRatesReport.pdf
2. Collins C, Anderson M, and Burus T. Original Sample Summary Report: National High School Sports-Related Injury Surveillance Study: 2022–23 School Year. Datalys Center for Sports Injury Research and Prevention. Accessed April 5 (2023).
3. Jastifer JR, McNitt AS, Mack CD, et al. Synthetic Turf: History, Design, Maintenance, and Athlete Safety. *Sports Health Multidiscip Approach*. 2019;11(1):84-90. doi:10.1177/1941738118793378
4. *Participation Statistics. NFHS MMS. (n.d.). Https://Members.Nfhs.Org/Participation_statistics*.
5. Dragoo JL, Braun HJ. The effect of playing surface on injury rate: a review of the current literature. *Sports Med Auckl NZ*. 2010;40(11):981-990. doi:10.2165/11535910-000000000-00000
6. Drakos MC, Taylor SA, Fabricant PD, Haleem AM. Synthetic playing surfaces and athlete health. *J Am Acad Orthop Surg*. 2013;21(5):293-302. doi:10.5435/JAAOS-21-05-293
7. O'Leary F, Acampora N, Hand F, O' Donovan J. Association of artificial turf and concussion in competitive contact sports: a systematic review and meta-analysis. *BMJ Open Sport Exerc Med*. 2020;6(1):e000695. doi:10.1136/bmjsem-2019-000695
8. Rennie DJ, Vanrenterghem J, Littlewood M, Drust B. Can the natural turf pitch be viewed as a risk factor for injury within Association Football? *J Sci Med Sport*. 2016;19(7):547-552. doi:10.1016/j.jsams.2015.07.009
9. Taylor SA, Fabricant PD, Khair MM, Haleem AM, Drakos MC. A review of synthetic playing surfaces, the shoe-surface interface, and lower extremity injuries in athletes. *Phys Sportsmed*. 2012;40(4):66-72. doi:10.3810/psm.2012.11.1989
10. Williams S, Hume PA, Kara S. A Review of Football Injuries on Third and Fourth Generation Artificial Turfs Compared with Natural Turf: *Sports Med*. 2011;41(11):903-923. doi:10.2165/11593190-000000000-00000
11. Winson DMG, Miller DLH, Winson IG. Foot injuries, playing surface and shoe design: Should we be thinking more about injury prevention. *Foot Ankle Surg Off J Eur Soc Foot Ankle Surg*. 2020;26(6):597-600. doi:10.1016/j.fas.2019.07.013
12. Balazs GC, Pavey GJ, Brelin AM, Pickett A, Keblish DJ, Rue JPH. Risk of Anterior Cruciate Ligament Injury in Athletes on Synthetic Playing Surfaces: A Systematic Review. *Am J Sports Med*. 2015;43(7):1798-1804. doi:10.1177/0363546514545864
13. Bushnell J, Dr. Zachary O. Binney, PhD, Emory University, Dr. Michael Goodman, MD MPH, Emory University. Exploring the Associations of Playing Surface and Lower Extremity Injuries Among National Football League Players. *Emory Univ Roll Sch Public Health*. Accessed October 27, 2024. https://etd.library.emory.edu/concern/etds/qn59q5437?locale=en
14. Venishetty N, Xiao AX, Ghanta R, Reddy R, Pandya NK, Feeley BT. Lower Extremity Injury Rates on Artificial Turf Versus Natural Grass Surfaces in the National Football League During the 2021 and 2022 Seasons. *Orthop J Sports Med*. 2024;12(8):23259671241265378. doi:10.1177/23259671241265378
15. Gould HP, Lostetter SJ, Samuelson ER, Guyton GP. Lower Extremity Injury Rates on Artificial Turf Versus Natural Grass Playing Surfaces: A Systematic Review. *Am J Sports Med*. 2023;51(6):1615-1621. doi:10.1177/03635465211069562
16. Loughran GJ, Vulpis CT, Murphy JP, et al. Incidence of Knee Injuries on Artificial Turf Versus Natural Grass in National Collegiate Athletic Association American Football: 2004-2005 Through 2013-2014 Seasons. *Am J Sports Med*. 2019;47(6):1294-1301. doi:10.1177/0363546519833925

17. Mack CD, Hershman EB, Anderson RB, et al. Higher Rates of Lower Extremity Injury on Synthetic Turf Compared With Natural Turf Among National Football League Athletes: Epidemiologic Confirmation of a Biomechanical Hypothesis. *Am J Sports Med*. 2019;47(1):189-196. doi:10.1177/0363546518808499
18. Xiao M, Lemos JL, Hwang CE, Sherman SL, Safran MR, Abrams GD. Increased Risk of ACL Injury for Female but Not Male Soccer Players on Artificial Turf Versus Natural Grass: A Systematic Review and Meta-Analysis. *Orthop J Sports Med*. 2022;10(8):23259671221114353. doi:10.1177/23259671221114353
19. Smoliga JM, Deshpande SK, Binney ZO. Interaction of Surface Type, Temperature, and Week of Season on Concussion Risk in the National Football League: A Bayesian Analysis. *Epidemiology*. 2023;34(6):807-816. doi:10.1097/EDE.0000000000001657
20. Williams JH, Akogyrem E, Williams JR. A Meta-Analysis of Soccer Injuries on Artificial Turf and Natural Grass. *J Sports Med*. 2013;2013:1-6. doi:10.1155/2013/380523
21. Howard M, Solaru S, Kang HP, et al. Epidemiology of Anterior Cruciate Ligament Injury on Natural Grass Versus Artificial Turf in Soccer: 10-Year Data From the National Collegiate Athletic Association Injury Surveillance System. *Orthop J Sports Med*. 2020;8(7):2325967120934434. doi:10.1177/2325967120934434
22. Kuitunen I, Immonen V, Pakarinen O, Mattila VM, Ponkilainen VT. Incidence of football injuries sustained on artificial turf compared to grass and other playing surfaces: a systematic review and meta-analysis. *eClinicalMedicine*. 2023;59:101956. doi:10.1016/j.eclinm.2023.101956
23. National Electronic Injury Surveillance System (NEISS). U.S. Consumer Product Safety Commission. Accessed September 6, 2024. https://www.cpsc.gov/Research--Statistics/NEISS-Injury-Data
24. DeFroda SF, Lemme N, Kleiner J, Gil J, Owens BD. Incidence and mechanism of injury of clavicle fractures in the NEISS database: Athletic and non athletic injuries. *J Clin Orthop Trauma*. 2019;10(5):954-958. doi:10.1016/j.jcot.2019.01.019
25. Kuczinski A, Newman JM, Piuzzi NS, et al. Trends and Epidemiologic Factors Contributing to Soccer-Related Fractures That Presented to Emergency Departments in the United States. *Sports Health*. 2019;11(1):27-31. doi:10.1177/1941738118798629
26. Meixner C, Loder RT. The Demographics of Fractures and Dislocations Across the Entire United States due to Common Sports and Recreational Activities. *Sports Health*. 2020;12(2):159-169. doi:10.1177/1941738119882930
27. Reiad TA, Peveri E, Dinh PV, Owens BD. Epidemiology of Shoulder Injuries Presenting to US Emergency Departments. *Orthopedics*. 2025;48(2):e81-e87. doi:10.3928/01477447-20250204-03
28. Dinh PV, Reiad TA, Peveri E, Marquis C, Gil JA. A 20-year national decline in wrist fractures: Unraveling trends and persistent challenges. *Hand Surg Rehabil*. Published online March 25, 2025:102151. doi:10.1016/j.hansur.2025.102151
29. Zaifman JM, Megalla M, Grace Z, et al. Orthopaedic Sports Injuries in an Aging Population: Current Trends and Future Projections. *Sports Health*. Published online January 29, 2025:19417381251314078. doi:10.1177/19417381251314078
30. Durand WM, Goodman AD, Giglio P, Etzel C, Owens BD. Epidemiology of Upper Extremity Soccer Injuries Among High School– and College-Aged Players in the United States: An Analysis of the 1999-2016 NEISS Database. *Sports Health*. 2018;10(6):552-557. doi:10.1177/1941738118795483
31. Painter DF, Ahn BJ, Byrne RA, et al. Upper extremity orthopedic softball injuries presenting to the emergency department: epidemiology across the lifespan. *Phys Sportsmed*. 2025;53(1):72-79. doi:10.1080/00913847.2024.2411574
32. US Consumer Product Safety Commission. 2023. NEISS Coding Manual. Available at: Https://Www.Cpsc.Gov/Cgibin/NEISSQuery/Data/Info%20Docs/2023%20NEISS%20Coding%20Manual.Pdf. Accessed December 3, 2024.
33. Jastifer JR, McNitt AS, Mack CD, et al. Synthetic Turf: History, Design, Maintenance, and Athlete Safety. *Sports Health*. 2019;11(1):84-90. doi:10.1177/1941738118793378
34. Venishetty N, Xiao AX, Ghanta R, Reddy R, Pandya NK, Feeley BT. Lower Extremity Injury Rates on Artificial Turf Versus Natural Grass Surfaces in the National Football League During the 2021 and 2022 Seasons. *Orthop J Sports Med*. 2024;12(8):23259671241265378. doi:10.1177/23259671241265378
35. Mack CD, Hershman EB, Anderson RB, et al. Higher Rates of Lower Extremity Injury on Synthetic Turf Compared With Natural Turf Among National Football League Athletes: Epidemiologic Confirmation of a Biomechanical Hypothesis. *Am J Sports Med*. 2019;47(1):189-196. doi:10.1177/0363546518808499
36. Dowling AV, Corazza S, Chaudhari AMW, Andriacchi TP. Shoe-surface friction influences movement strategies during a sidestep cutting task: implications for anterior cruciate ligament injury risk. *Am J Sports Med*. 2010;38(3):478-485. doi:10.1177/0363546509348374
37. Drakos MC, Hillstrom H, Voos JE, et al. The effect of the shoe-surface interface in the development of anterior cruciate ligament strain. *J Biomech Eng*. 2010;132(1):011003. doi:10.1115/1.4000118
38. Villwock MR, Meyer EG, Powell JW, Fouty AJ, Haut RC. Football playing surface and shoe design affect rotational traction. *Am J Sports Med*. 2009;37(3):518-525. doi:10.1177/0363546508328108
39. Villanueva NC, Chun IKH, Fujiwara AS, Leibovitch ER, Yamamoto BE, Yamamoto LG. Impact Deceleration Differences on Natural Grass Versus Synthetic Turf High School Football Fields. *Hawaii J Health Soc Welf*. 2024;83(1):4-9.
40. Sanchez-Sanchez J, Felipe JL, Hernandez-Martin A, et al. Influence of the artificial turf certification on physical performance and muscle damage in football players (QUALTURF PROJECT). *Sci Rep*. 2021;11:8625. doi:10.1038/s41598-021-88192-w

Authors

Timothy A. Reiad, BS, the Warren Alpert Medical School of Brown University, Providence, RI.

John D. Milner, MD, Resident of Orthopaedic Surgery at the Warren Alpert Medical School of Brown University in Providence, RI.

Peter V. Dinh, BS, Sports Medicine Research Fellow, the Warren Alpert Medical School of Brown University in Providence, RI.

John Pietro, BS, the Warren Alpert Medical School of Brown University in Providence, RI.

Rigel P. Hall, BS, Creighton University School of Medicine in Omaha, Nebraska.

Jonathan Liu, MD, Resident of Orthopaedic Surgery at the Warren Alpert Medical School of Brown University in Providence, RI.

Brett D. Owens, MD, University Orthopedics in East Providence, RI; Warren Alpert Medical School of Brown University in Providence, RI.

Stephen E. Marcaccio, MD, University Orthopedics in East Providence, RI, Warren Alpert Medical School of Brown University in Providence, RI.

Disclosures

Ethical Approvals: Ethical approval is not applicable for this article.

Disclaimer: The views expressed herein are those of the authors and do not necessarily reflect the views of the Warren Alpert Medical School or University Orthopedics.

Conflict of interest: BDO discloses the following: consulting or advisory relationship with CONMED Corporation and Vericel Corporation, as well as a patent with royalties paid by CONMED. All other authors have no conflicts of interest to disclose.

Funding Sources: This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Data Statement: Data not available. The authors do not have permission to share data.

Correspondence

Peter Dinh, BS

18 University Ave, Providence, RI 02906

peter_dinh@brown.edu

Demographic Analysis of Populations Accessing an Overdose Response Training Created at a College of Pharmacy

MICHAELA PACHECO, PharmD; ABIODUN OLOGUNOWA, MS, BPharm; ANITA JACOBSON, PharmD

ABSTRACT

OBJECTIVE: To analyze and compare demographics of two distinct populations accessing an online opioid overdose response training program hosted on two websites.

METHODS: A retrospective comparative analysis was completed using post-training survey data collected from October 2019 through October 2023. The training and survey were accessible through the University of Rhode Island and Rhode Island Department of Health websites. Demographics were compared between access points and to characteristics of populations at-risk for overdose.

RESULTS: 4,785 surveys were included. Participants accessing the training through the university website were more likely to be racial minorities and students. Participants accessing through the Department of Health were more likely to be gender minorities, low-income, and work in healthcare or trades. No differences in rurality or education level existed; both groups indicated satisfaction with training.

CONCLUSIONS: The same online overdose response training can reach different populations with demographic characteristics associated with increased overdose risk when made accessible through multiple access points.

KEYWORDS: naloxone; overdose; online training; opioid education; harm reduction; interdisciplinary collaboration

INTRODUCTION

The number of lives lost to drug overdose in the United States has increased over the last two decades, with over 107,000 lives lost to overdose annually from 2021 through 2023.[1-5] More than 75% of all overdose deaths are attributed to opioids, and the increase in synthetic opioids in the unregulated drug supply has caused a rapid and persistent rise in deaths from opioids since 2016.[3-6] The increased presence of synthetic opioids in non-opioid substances such as cocaine and methamphetamine has expanded the population of people who use drugs (PWUD) at risk for experiencing an opioid overdose beyond those who only use opioids.[6-8] Likewise, demographics of people with high risk for experiencing or responding to an overdose have shifted.[9-11] Within the last decade, all age groups 15 years of age and older, all race and Hispanic-origin groups and all genders (including transgender and gender non-conforming individuals) have experienced increases in fatal opioid overdoses.[2-6,12,13] The opioid crisis constitutes an ongoing public health emergency affecting diverse populations of people, underscoring the need for expansive, open-access harm reduction strategies.[16]

Numerous harm reduction efforts have been made on community, state, and federal levels to address the dynamic needs of PWUD and those responding to opioid overdoses. Many existing and effective harm reduction strategies are centered around improving access to naloxone, an opioid antagonist used to reverse overdoses, which can be administered by anyone.[17-19] Pharmacists and pharmacies have been integral in expanding naloxone distribution, with state legislation for co-prescribing naloxone with prescription opioids and statewide standing orders facilitating easier naloxone access through pharmacies.[20,21] Additionally, in 2023, the Food and Drug Administration (FDA) approved two naloxone nasal spray formulations over-the-counter (OTC), allowing for retail access at pharmacies without a prescription.[22,23] With increased naloxone distribution, it is necessary to ensure its appropriate and effective use through overdose response training.

Overdose education and naloxone distribution (OEND) programs combine naloxone distribution and training on overdose recognition, response, and naloxone administration. There are myriad benefits reported by people who participate in OEND programming, including changed attitudes and increased confidence with overdose recognition and naloxone administration.[24] While OEND programs are one of the most effective harm reduction strategies, barriers to engagement exist, and many PWUD report little to no OEND engagement, despite knowing about available services. Stigma, physical inaccessibility, and mistrust of people providing OEND education represent key barriers to OEND engagement.[25-29] A compelling strategy for mitigating access and stigma barriers is remote provision of overdose response education and mail-order distribution of naloxone.

The increased national death toll from opioid overdose has been reflected at the state level in Rhode Island.[30] In efforts to address barriers surrounding OEND engagement and utilize the effectiveness of OEND programming, an interdisciplinary team created the Community First Responder Program (CFRP) at the state university college of pharmacy in 2019.

The interprofessional team which created the CFRP was comprised of pharmacists, a pharmacy technician, pharmacy and nursing students and faculty, a licensed mental health counselor, and representatives from the College of Environmental and Life Sciences. The CFRP is a fully remote, open access online overdose response training program and wholesale pharmacy which distributes naloxone and other harm reduction supplies. The CFRP has been hosted and accessible on the university website (UNIV) since its inception.[31] In 2021, the Rhode Island Department of Health (RIDOH) fully funded the CFRP initiative and expanded access by hosting the training program and its survey on their harm reduction website, Prevent Overdose Rhode Island (DOH; https://preventoverdoseri.org/get-naloxone).[32] Since the program's creation at UNIV, and subsequent expansion by DOH, over 4,700 individuals have completed the training program and responded to its survey. In this paper, the demographics of people accessing the training through UNIV are compared to those of individuals accessing through DOH, and both are compared to pre-defined risk factors for experiencing or responding to an overdose.

METHODS

Study Aim

The aim of this study is to compare the demographics of two distinct populations (UNIV and DOH) completing an online overdose response training module based on predefined risk factors for experiencing or responding to an overdose. The goal is to expand current knowledge on overdose response education uptake and to inform development of strategies to broaden access to OEND programs.

Design and Setting

This is a retrospective comparative analysis of demographic data from individuals who completed an online overdose response training program and its post-survey. All data were voluntarily provided and de-identified prior to inclusion in analysis. The study was approved by the state university Institutional Review Board (IRB reference #2124391-2).

The CFRP and PORI are two internet-based harm reduction programs serving communities in Rhode Island. Both programs house the same online overdose response training program and post-survey. The public may freely access the training by visiting either the state university website (UNIV) or the state Department of Health's harm reduction website (DOH).[31,32]

Data Sources and Study Population

Post-training surveys from October 2019 to October 2023 submitted through UNIV and DOH access points were included in the study. Responses collected from both the UNIV and DOH platforms contain demographic information as well as respondents' satisfaction with and perceived benefits of the overdose response training module.

The post-training survey on both UNIV and DOH websites collected demographic information including gender identity, race/ethnicity, highest educational level achieved, primary employment type, and zip code of employment. Additionally, responses regarding the perceived benefits of and satisfaction with the training program were collected.

Responses were recorded as selections from a list of predetermined options, self-identification free text responses, or declining to respond. For gender identity, participants could select male, female, transgender, gender non-conforming, other (with free text response), or decline to respond. Race and ethnicity options included White, Black/African American, American Indian/Alaskan Native, Asian, Native Hawaiian/Pacific Islander, Hispanic/Latino, or other. Educational level options included less than high school, high school diploma/GED, some college/no degree, associate's, bachelor's, master's or doctoral degree/equivalent, or other. Data on primary profession and principal employment setting were collected through free text responses.

Data Organization

To compare population demographics from the UNIV and DOH websites to demographics of populations with increased risk in Rhode Island, "risk" first needed to be defined. Current literature assessing demographics of individuals at increased risk in the United States indicates that those of lower socioeconomic status, in rural areas, racial and gender minorities, those with a high school degree or lower level of education (used as a proxy for health literacy), and certain age groups are at greater risk of experiencing a fatal opioid overdose than others.[1-7,9-15]

To prepare the post-training survey data set for analysis, responses were further classified as follows: zip codes were matched for rurality using the definition of rurality set by RIDOH; zip codes were matched for area income status using median household income data from the Rhode Island Department of Labor and Training, with towns classified as either "low-income" (bottom 20th percentile of cities/towns in the state), or "other" (above the 20th percentile); primary profession setting was categorized using the United States Bureau of Labor Statistics Standard Occupation Codes, then further refined using the United States Office of Personnel Management Classification of General Schedule Positions.[33-36]

For gender identity, gender minorities (transgender, gender non-conforming, and other as identified by free text) were compared to cis-gendered individuals (man or woman). For racial identity, White individuals were compared to racial minorities, defined as all other races/ethnicities besides White, including mixed-race (any combination of two or more racial identities). Education level, used as a proxy for health literacy, was compared as less than high school versus all other levels/degrees achieved above high school. In

terms of employment type, healthcare professionals were compared to other professionals, trade/craft/labor workers, students, or "other" defined as retired, unemployed, receiving disability, or stay-at-home parent. Because UNIV is hosted and promoted on the state university website, an additional analysis was conducted to compare students to healthcare professionals, other professionals, trade/craft/labor workers, or "other" employment types.

STATISTICAL ANALYSIS

A total of 4,785 surveys (UNIV n=4097; DOH n=688) with partially and/or fully completed responses were included in the analysis. Descriptive statistics were initially applied to determine the percentages of each response type, including unknown or missing responses, for each data set from their respective access points. Blank responses were excluded from analysis on a question-by-question basis, and the number and percentage of non-responses per question are reported in the results tables.

To identify statistically significant differences between the two data sets by access point (UNIV versus DOH), Chi-square tests were performed to assess differences in population demographics based on access point. If Chis-square assumptions were not met, Fisher's exact tests were applied. A simple univariate logistic regression model was used to estimate the association between access points and demographic variables, reporting odds ratio (OR) and 95% confidence intervals. Statistical analyses were conducted using SAS version 9.4.

RESULTS

Descriptive statistics of the two populations analyzed are presented in **Table 1**. Statistically significant differences were observed between populations accessing the training and survey through UNV compared to DOH in terms of gender (χ^2 = 20.4, p< 0.0001), race (χ^2 = 52.0, p< 0.0001), income (low-income vs. other; χ^2 = 21.2, p< 0.0001), and profession (χ^2 = 457.4, p<0.0001)) as presented in **Table 2**.

When comparing demographics of individuals accessing the survey through UNIV compared to DOH, individuals accessing through UNIV were less likely to be gender minorities (OR 0.319; 95% CI: 0.189–0.538) but were twice likely to be racial minorities (OR 2.099;95% CI: 1.710–2.576) compared to DOH respondents. Additionally, UNIV participants were less likely to work in low-income areas (OR 0.589;95% CI: 0.469–0.739) and less likely to be non-healthcare professionals (OR 0.424; 95% CI 0.345–0.521) compared to DOH participants. UNIV participants were nearly nine times more likely to be students than healthcare professionals (OR 9.909; 95% CI: 6.615–14.841) and were less likely to be a trade/craft/or labor worker than healthcare professional (OR 0.362; 95% CI 0.255–0.513), or to be retired, unemployed,

Table 1. Demographic characteristics of survey respondents overall and by data source.

	Overall N=4785, (%)	UNIV N=4097, (%)	DOH N=688, (%)
Gender			
Gender Minority	64 (1.3)	42 (1.0)	22 (3.2)
Other	4628 (96.7)	3965 (96.8)	663 (96.4)
Unknown/missing	93 (1.9)	90 (2.2)	<5 (0.4)
Race			
Racial minority	1403 (29.3)	1278 (31.2)	125 (18.2)
Other (White)	3288 (68.7)	2728 (66.6)	560 (81.4)
Unknown/missing	94 (2.0)	91 (2.2)	<5 (0.4)
Education			
Less than high school	68 (1.4)	55 (1.3)	13 (1.9)
High school and above	4531 (94.7)	3882 (94.8)	649 (94.3)
Unknown/missing	186 (3.9)	160 (3.9)	26 (3.8)
Income level			
Low-income	558 (11.7)	360 (8.8)	198 (28.8)
Other income	977 (20.4)	738 (18.0)	239 (34.7)
Unknown/missing	3250 (67.9)	2999 (73.2)	251 (36.5)
Location			
Rural	274 (5.7)	203 (5.0)	71 (10.3)
Non-rural	1793 (37.5)	1271 (31.0)	522(75.9)
Unknown/missing	2718 (56.8)	2623 (64.0)	95 (13.8)
Primary Profession			
Healthcare professional	1654 (34.6)	1410 (34.4)	244 (35.5)
Professionals	773 (16.2)	549 (13.4)	224 (32.6)
Trade, craft,	170 (3.6)	115 (2.8)	55 (8.0)
Student	1573 (32.9)	1546 (37.7)	27 (3.9)
Other	123 (2.6)	73 (1.8)	50 (7.3)
Unknown/missing	492 (10.3)	404 (9.9)	88 (12.8)

Note: The sum of some percentages are greater than 100%, figures were rounded up. The participants for variables with fewer than 5 responses were not reported.

Table 2. Differences in Proportions of Gender, Race, Income, Residence and Profession Demographics within UNIV relative to DOH

Demographics	UNIV vs. DOH [Chi-square, χ^2, (p-value)]
Gender (minority vs other)	20.4 (<0.0001*)
Race	52.0 (<0.0001*)
Income	21.2 (<0.0001*)
Residence	1.2 (0.2753)
Education	1.2 (0.2636)
Primary Profession	457.4 (<0.0001*)

*Significance level p≤0.05

receiving disability, or a stay-at-home parent (OR 0.253; 95% CI 0.172–0.371).

When comparing the student population to other professionals, UNIV respondents were significantly less likely to be healthcare professionals, other professionals, trade/craft/labor workers, or "other". The results for differences in rurality and education level (and therefore, health literacy) based on access point were not statistically significant. Complete results are presented in **Tables 3** and **4**.

Participants across both access points were satisfied with the training program and found it to be useful. Of all participants, the majority reported that they were satisfied with the training (97.30%), found the training to be beneficial (96.26%), and found the training to be applicable (95.68%). Statistically significant differences were found in training perceptions from UNIV respondents compared to DOH respondents in terms of training satisfaction (χ^2 = 7.9, p=0.0190), training benefit (χ^2 = 19.3, p< 0.0001), and training applicability (χ^2 = 10.4, p = 0.0055). Results for perceived utility and satisfaction with the training content are presented in **Tables 5** and **6**.

Table 3. Relationships between access points and population demographics

Demographics	UNIV vs. DOH (Odds ratio, [95% confidence interval (CI)])
Gender (Minority vs Other)	**0.319 [0.189, 0.538]**
Race (Minority vs Other (White)	**2.099 [1.710, 2.576]**
Income (Low vs Other)	**0.589 [0.469, 0.739]**
Residence (Rural vs non-rural)	1.174 [0.880, 1.567]
Education (High school and above vs Less than high school)	1.415 [0.769, 2.604]
Primary Profession	
Professional vs. Healthcare Professional	**0.424 [0.345, 0.521]**
Student vs. Healthcare Professional	**9.909 [6.615, 14.841]**
Trade Worker vs. Healthcare Professional	**0.362 [0.255, 0.513]**
Other vs. Healthcare Professional	**0.253 [0.172, 0.371]**

Statistically significant results are **bolded**.

Table 4. Additional analysis of primary professions compared to students

Primary Profession	UNIV vs. DOH (Odds ratio, [95% CI])
Healthcare Worker vs. Student	**0.101 [0.067, 0.151]**
Professional vs. Student	**0.043 [0.028, 0.065]**
Trade Worker vs. Student	**0.037 [0.022, 0.060]**
Primary profession (Other vs Student)	**0.025 [0.015, 0.043]**

Statistically significant results are **bolded**.

Table 5. Satisfaction with training quality, perceived utility benefit and perceived applicability reported by respondents.

Response	Overall n=4785 (%)	UNIV n=4097 (%)	DOH n=688 (%)
Training quality			
Satisfied	4502 (97.30)	3844 (97.12)	658 (98.36)
Neutral	104 (2.25)	98 (2.48)	6 (0.90)
Dissatisfied	21 (0.45)	16 (0.40)	5 (0.75)
No response	158	139	19
Training benefit			
Agree	4453 (96.26)	3827 (96.77)	626 (93.30)
Neutral	152 (3.29)	112 (2.83)	40 (5.96)
Disagree	21 (0.45)	16 (0.40)	5 (0.75)
No response	159	142	17
Training application			
Agree	4424 (95.68)	3798 (96.03)	626 (93.30)
Neutral	182 (3.93)	142 (3.59)	40 (5.96)
Disagree	20 (0.43)	15 (0.38)	5 (0.75)
No response	159	142	17
Willingness to refer others to training program			
Yes	4573 (99.18)	3912 (99.24)	661 (98.80)
No	38 (0.82)	30 (0.76)	8 (1.20)
No Response	174	155	19

Table 6. Differences in survey responses for quality, benefit, application, and likelihood to refer others to training program within UNIV relative to DOH

Demographics	UNIV vs. DOH [Chi-square, χ^2, (p-value)]
Training quality	7.9 (0.0190)
Training benefit	19.3 (<0.0001)
Training application	10.4 (0.0055)
Would refer others to training	1.3 (0.2501)

*Significance level p≤0.05

DISCUSSION

To the authors' knowledge, this is the first study analyzing and comparing demographics of populations accessing an overdose response training created at a college of pharmacy. We found significant differences in the demographics of both populations accessing the training through its two access points, and individuals across both access points perceived the training to be useful and satisfactory. Differences in demographics between the two unique populations may be attributed to different advertising strategies used to attract participants to each website. The CFRP website is advertised on the URI website and campus, and the DOH PORI website is advertised through both online and published materials. Although some demographics associated

with at-risk populations were not significantly represented in the findings (rural versus non-rural settings and education level), the results of this study can be used to guide development and implementation of future trainings, as well as expansion of existing programs to reach the growing number of at-risk populations.

Though OEND programs represent a necessary and effective harm reduction strategy, several studies have assessed how OEND operations can be improved.[25-28] A qualitative study by Enich, et al 2023 sought to gain understanding of the perspectives of PWUD and harm reductionists on what an ideal OEND program would look like. Many of the PWUD interviewed reported little to no OEND engagement, despite knowing about available OEND services. Lack of engagement can be attributed to barriers like stigma, accessibility, and mistrust of people providing overdose response education. There are myriad ways to address barriers surrounding engagement. The CFRP mitigates access barriers by design, anyone with internet can access it. Additionally, since it can be completed remotely, it is a discreet option for people who may not access physical OEND programs because of stigma. Lastly, the overdose response training module was written and designed by a team of healthcare professionals including pharmacists, pharmacy technicians, nurses, and a licensed mental health counselor.

Interdisciplinary collaboration is a key component of developing robust and sustainable OEND programs.[26,27] The program was started by an interdisciplinary team, with contributors and users coming from diverse professional and educational backgrounds. Wenger, et al 2022 completed a study to identify best practice recommendations for community-based OEND programs.[29] Researchers assembled a team of OEND experts from diverse backgrounds (including syringe service program workers, health departments, and OEND researchers), generated a list of best practices, and ranked them. Among increased availability and distribution of naloxone itself, needs-based naloxone training, training of laypeople to provide naloxone education, and provision of overdose response information and educational materials were highlighted as best practices. The CFRP achieves all of these, with the added benefit of being hosted online and open for access at any time. Additionally, Wenger, et al. identified naloxone outreach and marketing efforts to be an important best practice.[29] This represents the need to increase awareness of the availability of the training, and other online-only OEND programs, in order to reach the at-risk populations identified in the study.

The training program is important because it can be accessed by anyone, spanning from professionals to students, community laypeople, and PWUD. Additionally, it is not a scheduled webinar and can be completed at any time without the need for an active facilitator. Previous studies evaluating opioid overdose response trainings have focused on the impact of providing training to healthcare professionals, first responders, and people who use drugs in the forms of webinars and short courses. The CFRP is unique in that it is not specific to any one audience and does not need to be completed at a specific time, with the goal of providing comprehensive overdose response education to anyone who sees its value.

Limitations

This study focused on characterizing and comparing demographics of two populations accessing an online overdose response training program based on pre-defined at-risk demographics. Importantly, the location data collected (zip codes) and subsequent data organization (rurality and income coding) do not necessarily reflect the areas in which respondents live, as zip codes provided were for addresses of employment. For the Rhode Island overdose death data, it is important to note that Rhode Island residents who died of an overdose outside of the state were not captured or included.

The training program does not include a pre-module survey at this time, so change in attitudes before and after completing the training were not assessed. Additionally, while the training program is offered in both English and Spanish, the survey was only published in English, potentially missing data from Spanish-speaking participants. However, over the four-year data collection period, only nine requests for harm reduction supplies were submitted through the mail order that is linked to the program. Therefore, we suspect uptake from Spanish-speaking individuals to be low. Furthermore, it is important to recognize that the post-training survey is entirely voluntary and thus it is unknown how many individuals completed the training but did not complete the survey. Lastly, although the training is open access, it is internet-based, therefore it is not available to individuals without internet access.

CONCLUSION

With the expansion of populations at-risk for experiencing or responding to an opioid overdose, it is necessary to make high-quality overdose response training freely available. The same overdose response training was hosted at two distinct access points and advertised to different populations using different strategies. The populations accessing the training through its two access points were distinctly different. Results establish that hosting a training created by an interprofessional team on different websites can attract different populations with demographic characteristics associated with increased overdose risk and expand the reach of OEND programming.

References

1. Mattson CL, Tanz LJ, Quinn K, Kariisa M, Patel P, Davis N. Trends and geographic patterns in drug and synthetic opioid overdose deaths - United States, 2013–2019. Centers for Disease Control and Prevention. February 12, 2021. Accessed May 6, 2024. https://www.cdc.gov/mmwr/volumes/70/wr/mm7006a4.htm?s_cid=mm7006a4_w.
2. Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System, Mortality 2018-2022 on CDC WONDER Online Database, released in 2024. Data are from the Multiple Cause of Death Files, 2018-2022, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Available at: http://wonder.cdc.gov/ucd-icd10-expanded.html. Accessed on May 6, 2024.
3. Hedegaard H, Miniño AM, Spencer MR, Warner M. Drug overdose deaths in the United States, 1999–2020. NCHS Data Brief, no 428. Hyattsville, MD: National Center for Health Statistics. 2021. DOI: https://dx.doi.org/10.15620/cdc:112340.
4. Spencer MR, Garnett MF, Miniño AM. Drug overdose deaths in the United States, 2002-2022. NCHS Data Brief, no 491. Hyattsville, MD: National Center for Health Statistics. 2024. doi:10.15620/cdc:135849.
5. Ahmad FB, Cisewski JA, Rossen LM, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. 2024.
6. Rudd RA, Seth P, David F, Scholl L. Increases in Drug and Opioid-Involved Overdose Deaths — United States, 2010–2015. MMWR Morb Mortal Wkly Rep 2016;65:1445–1452. doi: http://dx.doi.org/10.15585/mmwr.mm655051e1.
7. Jones CM, Einstein EB, Compton WM. Changes in Synthetic Opioid Involvement in Drug Overdose Deaths in the United States, 2010-2016. JAMA. 2018 May 1;319(17):1819-1821. doi: 10.1001/jama.2018.2844. PMID: 29715347; PMCID: PMC6583033.
8. Wagner KD, Fiuty P, Page K, Tracy EC, Nocera M, Miller CW, Tarhuni LJ, Dasgupta N. Prevalence of fentanyl in methamphetamine and cocaine samples collected by community-based drug checking services. Drug Alcohol Depend. 2023 Nov 1;252:110985. doi: 10.1016/j.drugalcdep.2023.110985. Epub 2023 Oct 5. PMID: 37826988; PMCID: PMC10688611.
9. Bandara S, Byrne L, Berman V, Hurst A, King D, Gibbons JB, Sugarman OK, Livingston A, Kerins L, Hulsey EG, Alves A, Saloner B. Harm Reduction and Treatment Among People at High Risk of Overdose. JAMA Netw Open. 2024 Aug 1;7(8):e2427241. doi: 10.1001/jamanetworkopen.2024.27241. PMID: 39133486; PMCID: PMC11320172.
10. Altekruse SF, Cosgrove CM, Altekruse WC, Jenkins RA, Blanco C. Socioeconomic risk factors for fatal opioid overdoses in the United States: Findings from the Mortality Disparities in American Communities Study (MDAC). *PLoS One*. 2020;15(1):e0227966. Published 2020 Jan 17. doi:10.1371/journal.pone.0227966
11. Britz JB, O'Loughlin KM, Henry TL, et al. Rising Racial Disparities in Opioid Mortality and Undertreatment of Opioid Use Disorder and Mental Health Comorbidities in Virginia. *AJPM Focus*. 2023;2(3):100102. Published 2023 Apr 27. doi:10.1016/j.focus.2023.100102
12. Medley G, Liparin RN, Bose J, Cribb DS, Kroutil LA, McHenry, G. Sexual orientation and estimates of adult substance use and mental health: results from the 2015 National Survey on Drug Use and Health. NSDUH Data Review. Available at: http://samhsa.gov/data.
13. Keuroghlian AS, Reisner SL, White JM, Weiss RD. Substance use and treatment of substance use disorders in a community sample of transgender adults. Drug Alcohol Depend. 2015 Jul 1;152:139-46. doi: 10.1016/j.drugalcdep.2015.04.008.
14. Stormacq C, Van den Broucke S, Wosinski J. Does health literacy mediate the relationship between socioeconomic status and health disparities? Integrative review, Health Promotion International, 2019 Oct. 34;5:e1-17. doi:10.1093/heapro/day062
15. Garcia-Codina O, Juvinyà-Canal D, Amil-Bujan P, Bertran-Noguer C, González-Mestre MA, et al. Determinants of health literacy in the general population: results of the Catalan health survey. BMC Public Health. 2019 Aug 16;19(1):1122. doi: 10.1186/s12889-019-
16. Administration for Strategic Preparedness & Response. Renewal of determination that a public health emergency exists. 2023 Dec21. *PHE Declarations*. https://aspr.hhs.gov/legal/PHE/Pages/Opioid-21Dec2023.aspx
17. Naloxone. In: Clinical Pharmacology [database on the Internet]. Tampa (FL): Elsevier; 2017 [cited 2024 Jun 26]. Available from: www.clinicalpharmacology.com. Subscription required to view.
18. Naloxone [package insert]. Richmond, VA: Kaleo, Inc; 2022.
19. Lifesaving naloxone. CDC. 2024. https://www.cdc.gov/stopoverdose/caring/naloxone.html#cdc_generic_section_4-who-should-carry-naloxone. Accessed 2024 Jun 25.
20. Green TC, Davis C, Xuan Z, Walley AY, Bratberg J. Laws mandating coprescription of naloxone and their impact on naloxone prescription in five US states, 2014-2018. Am J Public Health. 2020; doi: 10.2105/AJPH.2020.305620.
21. Xuan Z, Walley AY, Yan S, Chatterjee A, Green TG, Pollini RA. Pharmacy Naloxone Standing Order and Community Opioid Fatality Rates Over Time. JAMA Netw Open. 2024 Aug 1;7(8):e2427236. doi: 10.1001/jamanetworkopen.2024.27236. PMID: 39207758; PMCID: PMC11362859.
22. Food and Drug Administration. FDA approves first over-the-counter naloxone nasal spray. 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-first-over-counter-naloxone-nasal-spray. Accessed 2024 Jun 25.
23. Food and Drug Administration. FDA approves second over-the-counter naloxone nasal spray product. 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-second-over-counter-naloxone-nasal-spray-product. Accessed 2024 Jun 25.
24. Razaghizad A, Windle SB, Filion KB, Gore G, Kudrina I, Paraskevopoulos E, Kimmelman J, Martel MO, Eisenberg MJ. The Effect of Overdose Education and Naloxone Distribution: An Umbrella Review of Systematic Reviews. Am J Public Health. 2021 Aug;111(8):e1-e12. doi: 10.2105/AJPH.2021.306306. Epub 2021 Jul 2. PMID: 34214412; PMCID: PMC8489614.
25. Enich M, Flumo R, Campos S, et al. Overdose education and naloxone distribution program design informed by people who use drugs and naloxone distributors. *Prev Med Rep*. 2023;35:102374. Published 2023 Aug 19. doi:10.1016/j.pmedr.2023.102374
26. Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ*. 2013;346:f174. Published 2013 Jan 30. doi:10.1136/bmj.f174
27. Bangham C, Cunnington S, Fielman S, Hurley M, Gergerian S, Greece JA. Using formative evaluation of a community-based opioid overdose prevention program to inform strategic communication for adoption, implementation, and sustainability. *BMC Public Health*. 2023;23(1):341. Published 2023 Feb 15. doi:10.1186/s12889-023-15229-2
28. Murza G, Meier C, Ward L, O'Shay S, Faldmo D. Addressing the Opioid Crises: An Evaluation of the Community Opioid Education Pilot Program. Outcomes and Impact Quarterly, 2023;3(3). doi: https://doi.org/10.59620/2995-2220.1061
29. Wenger LD, Doe-Simkins M, Wheeler E, Ongais L, Morris T, Bluthenthal RN, Kral AH, Lambdin BH. Best practices for community-based overdose education and naloxone distribution programs: results from using the Delphi approach. Harm Reduct J. 2022 May 28;19(1):55. doi: 10.1186/s12954-022-00639-z. PMID: 35643444; PMCID: PMC9145109.

30. Rhode Island Department of Health. Overdose fatalities. RIDOH Drug Overdose Surveillance Data Hub. Available at: https://ridoh-drug-overdose-surveillance-fatalities-rihealth.hub.arcgis.com. Accessed May 6, 2024.
31. Community First Responder Program. https://web.uri.edu/cfrp/ (2024). The University of Rhode Island. Accessed 2024 Apr 8.
32. Prevent Overdose RI. https://preventoverdoseri.org/get-naloxone (2024). Rhode Island Department of Health. Accessed 2024 Apr 8.
33. Rhode Island Department of health. Defining Rural Rhode Island. 2022. Available at: https://health.ri.gov/publications/definitions/2022Rural-definition.pdf. Accessed May 6, 2024.
34. Rhode Island Department of Labor and Training. RI City & Town Income from American Community Survey 5-Year Estimates 2017-2021. Available at: https://dlt.ri.gov/sites/g/files/xkgbur571/files/documents/pdf/lmi/towninc.pdf. Accessed May 6, 2024.
35. United States Bureau of Labor Statistics. 2018 Standard Occupational Classification System. Available at: https://www.bls.gov/soc/2018/major_groups.htm. Accessed May 6, 2024.
36. United States Office of Personnel Management. Handbook of Occupational Groups and Families. December 2018. Available at: https://www.opm.gov/policy-data-oversight/classification-qualifications/classifying-general-schedule-positions/occupationalhandbook.pdf. Accessed May 6, 2024.

Authors

Michaela Pacheco, PharmD, T32 Post-Doctoral Research Fellow, The Miriam Hospital, Providence, RI; University of Rhode Island, College of Pharmacy, Kingston, RI.

Abiodun Ologunowa, MS, BPharm, University of Rhode Island, College of Pharmacy, Kingston, RI.

Anita Jacobson, PharmD, University of Rhode Island, College of Pharmacy, Kingston, RI.

Disclosures

Funding: The research in this publication was supported by the National Institute on Drug Abuse of the National Institutes of Health under award 5T32DA013911-20. Author MP is supported by this grant award and contributed to the study design, data collection, organization, and analysis, and writing of this publication.

Disclaimer: The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data: Data sets used for the study are available from the corresponding author upon reasonable request.

All tables were compiled using original data from the study survey.

Financial: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics Approval: This is a retrospective comparative analysis of demographic data from individuals who completed an online overdose response training program and its post-survey. All data were voluntarily provided and de-identified prior to inclusion in analysis. The study was approved by the University of Rhode Island Institutional Review Board (IRB reference #2124391-2).

Correspondence

Michaela Pacheco
7 Greenhouse Ln #295L
Kingston, RI 02881
401-332-9056
mlpach@uri.edu

Assessing the Utilization and Value of the Prescription Drug Monitoring Program Prescriber Report, Rhode Island

TAYLOR J. MELLO, MPH; ADAM Z. NITENSON, PhD; JANE FERNANDEZ, PharmD

BACKGROUND

The Rhode Island Prescription Drug Monitoring Program (RI PDMP) collects data for controlled substance prescriptions (Schedule II – V) and opioid antagonists into a centralized database.[1] These data can then be used by prescribers and pharmacists in the active treatment of their patients. The RI PDMP's primary functions are to identify high-risk prescribing patterns such as overprescribing, dangerous drug combinations, and controlled substance prescription dispensations from multiple pharmacies and providers, to name a few.

In January 2022, the RI PDMP introduced an individualized electronic prescriber report. This report is provided quarterly to each prescriber in the state who has an active PDMP account, a defined role and specialty, and has written at least one opioid, sedative, or stimulant prescription in the designated lookback period (typically six months). This enhanced, personalized report provides prescribers a snapshot of their prescribing history and includes helpful metrics such as prescribing patterns for opioids, buprenorphine, sedatives, and stimulants, as well as how these values compare to those of their peers. The report also presents information on patients at potentially elevated risk of overdose due to overlapping therapies, patients with multiple providers, high morphine milligram equivalent (MME) thresholds, and patient search activity, including searches performed by authorized delegate(s) on the prescriber's behalf.

The primary intent of the prescriber report is to provide prescribers with insight into their own prescribing patterns in relation to their peers, serving as a supportive tool in clinical decision-making rather than a form of administrative oversight. In January 2025, the RI PDMP conducted a survey to both examine prescriber utilization of the report and to assess changes in prescribing practices in response to the report.

METHODS

This analysis used data from a survey sent out in January 2025 to all prescribers in Rhode Island that are registered with the Rhode Island Prescription Drug Monitoring Program (PDMP). The survey was constructed and tested by members of the PDMP team at the Rhode Island Department of Health (RIDOH) before dissemination. The survey was sent out to 4,588 prescriber emails via a REDCap participation list and was available to participants for one month.

Data regarding respondent demographics, such as sex at birth, years of practice, specialty type, etc., were reported, as well as responses to questions assessing respondents understanding, perception, and utilization of the prescriber report. Respondents who reported being unfamiliar with the prescriber report were excluded from the analysis. Results were stratified by respondent workplace. Using thematic analysis for open response questions, answers were sorted into appropriate categories and were reviewed by two PDMP team members for accuracy. Categories with counts fewer than five were suppressed to protect the confidentiality of individual identities per the RIDOH Small Numbers Policy.[2]

RESULTS

In total, 184 prescribers responded to the survey. From this sample, 139 (75.5%) reported that they were familiar with the report (e.g., knew what the report was, had heard about the report, etc.). Of these 139 respondents included in the analysis, 86 (61.9%) had 15+ years of experience in their field [**Table 1**]. Just over half (n=75, 54.0%) of respondents worked in an outpatient setting (e.g., primary care, telehealth, community center), 46 (33.1%) worked in an inpatient setting (e.g., hospitals, skilled nursing facilities), and 18 (12.9%) worked in other settings (e.g., academic medical centers, director and consultant positions). Physicians made up 62.6% (N=87) of respondents, and 43 (30.9%) respondents specialized in primary care [**Table 1**].

Nearly 80% (N=111) of respondents included in the analysis stated that they have viewed the prescriber report. A higher proportion of inpatient respondents reported viewing compared to outpatient respondents (84.7% vs 78.7%, respectively; **Table 2**). When asked about frequency of access, 23% of all respondents stated that they "Never/Rarely" view the report, 33.1% of all respondents reported "Sometimes" viewing the report, and 21.6% reported they "Often/Always" view the report. These responses did not significantly differ by work setting. Respondents that stated they check the report, but answered "Never/Rarely" when asked about frequency may have viewed the report once or twice but do not regularly check the report. When asked about barriers that might prevent a respondent from viewing the report, 10.1% reported time constraints, 5% reported workload, and 8.6% reported that the prescriber

Table 1. Respondent Demographics

Demographic	N (%)
Years of Experience	
<5	12 (8.63%)
5 to <10	16 (11.5%)
10 to <15	25 (18.0%)
15+	86 (61.9%)
Place of work	
Inpatient	46 (33.1%)
Outpatient	75 (54.0%)
Other	18 (12.9%)
Prescriber Type	
Physician	87 (62.6%)
Nurse Practitioner/Clinical Nurse Specialist	46 (33.1%)
Other	6 (4.32%)
Prescriber Specialty	
Emergency Medicine/Urgent Care	10 (7.91%)
Primary Care	43 (30.9%)
High Prescribing Physicians[a]	8 (5.76%)
Pediatrics	11 (7.91%)
Psychiatry	22 (16.6%)
Surgical/Wound Care	6 (4.32%)
Other	25 (18.0%)
Missing	12 (8.63%)

[a] High Prescribing Clinicians include prescribers specializing in oncology, hospice, palliative care, and pain management.

report does not feel relevant to their practice [**Table 2**].

Of the respondents, 83 (59.7%) found the prescriber report to be useful to their practice. A slightly higher proportion of inpatient respondents found the report to be useful compared to outpatient respondents (60.8% and 54.7%, respectively; **Table 3**). Respondents found that the average number of opioids, stimulants, and benzodiazepines dispensed per

Table 2. Assessing respondents' capacity to view the report.

	Type of work setting			Total
	Outpatient (N=75)	Inpatient (N=46)	Other (N=18)	
Do participants view the prescriber report?				
Yes	59 (78.7%)	39 (84.7%)	13 (72.2%)	111 (79.9%)
Frequency of viewing report				
Never/Rarely	15 (20.0%)	12 (26.0%)	5 (27.8%)	32 (23.0%)
Sometimes	24 (32.0%)	16 (34.7%)	6 (33.3%)	46 (33.1%)
Often/Always	18 (24.0%)	10 (25.6%)	<5	30 (21.6%)
Barriers to viewing the report?[a]				
Time constraints	6 (8.0%)	<5	<5	14 (10.1%)
Workload	5 (6.67%)	<5	<5	7 (5.04%)
Not Relevant	6 (8.0%)	<5	<5	12 (8.63%)
Participants felt confident in their understanding of the report				
Yes	55 (73.3%)	33 (71.7%)	12 (66.6%)	100 (71.9)

[a] Categories are not mutually exclusive.

Table 3. Assessing the value of the report in respondents' practice

	Type of work setting			Total
	Outpatient (N=75)	Inpatient (N=46)	Other (N=18)	
Do participants find the report useful?				
Yes	41 (54.7%)	28 (60.8%)	14 (77.8%)	83 (59.7%)
What reporting metrics are most useful?[a]				
Avg number of opioid RXs dispensed per patient	23 (16.5%)	11 (7.91%)	5 (3.59%)	39 (28.1%)
Number of patient report requests	6 (4.31%)	10 (7.19%)	<5	19 (13.7%)
Avg daily MME for opioids dispensed per patient	18 (12.9%)	5 (3.59%)	<5	25 (18.0%)
Avg number of stimulant RXs dispensed per patient	21 (15.1%)	8 (5.75%)	7 (5.03%)	36 (26.9%)
Avg number of benzodiazepine RXs dispensed per patient	21 (15.1%)	9 (6.47%)	6 (4.31%)	36 (25.9%)
Dangerous medication combinations	22 (15.8%)	17 (12.2%)	6 (4.31%)	45 (32.4%)
Patients exceeding multiple provider thresholds	23 (16.5%)	14 (10.1%)	5 (3.59%)	42 (30.2%)
Number of unique patients	8 (5.75%)	5 (3.59%)	<5	14 (10.1%)
Avg number of controlled substances dispensed per patient	15 (10.8%)	9 (6.47%)	3 (2.15%)	27 (19.4%)
Avg days' supply of controlled substances dispensed per patient	10 (7.19%)	7 (5.03%)	<5	18 (13.0%)
Top medications prescribed	14 (10.1%)	8 (5.75%)	<5	26 (18.7%)
Did participants change their prescribing practices after viewing the report?				
Yes	11 (14.7%)	7 (15.2%)	<5	20 (14.4%)

[a] Categories are not mutually exclusive.

patient, as well as tallies of dangerous medication combinations and the number of patients exceeding multiple provider thresholds to be the most useful metrics reported. This differed by work setting, as less than 7% of inpatient respondents found the average number of stimulant and benzodiazepine prescriptions dispensed per patient to be as useful to their practice, compared to just over 15% of outpatient respondents [**Table 3**]. On top of this, nearly 13% of outpatient respondents found the average daily MME for opioids dispensed per patient to be a useful metric, compared to only approximately 4% of inpatient respondents. Nearly 15% (N=20) of all respondents reported changing their prescribing practice after viewing the prescriber report. This did not differ by work setting [**Table 3**].

DISCUSSION

Overall, the majority of the respondents had viewed the report, which aligns with one of the main goals of the survey. Specifically, 80% of the respondents reported viewing the report and over half of respondents reported viewing the report sometimes/often/always and found the report to be useful to their practice.

While greater than 50% of respondents found the prescriber report to be useful to their practice, the usefulness of specific metrics varied by workplace setting. A higher proportion of outpatient respondents found the average number of opioids, stimulants and benzodiazepines dispensed per patient, dangerous medication combination metric, and average daily MME for opioid patients metric more useful in their practice compared to inpatient respondents. Outpatient providers are most likely to see patients on a continuous basis and therefore dispense these medications regularly, while inpatient prescribers typically prescribe on an acute basis.

Several barriers to viewing the report were identified, with time constraints emerging as a significant barrier particularly among prescribers in outpatient settings. Of note, outpatient prescribers who identified community health centers as their primary work setting cited workload and time limitations as primary obstacles of engaging with the report (Results not shown due to RIDOH's Small Numbers Policy).

Relevance to practice was another commonly mentioned barrier. Prescribers who listed their specialty as emergency medicine noted that the nature of their practice is characterized by unique circumstances such as trauma/injury, and unpredictable patient populations made it difficult to effectively assess their prescribing patterns. Due to the acute and varied nature of their patient cases, they found it challenging to compare their prescribing habits with those of their peers. Similarly, providers who specialize in treating specific patient populations such as end of life/palliative care indicated that they did not find any significant value in the report. This is because their patients often require medications for symptom management such as pain and anxiety that typically involve controlled substances. As a result, these providers noted that the reports may not offer meaningful insights, since their prescribing practices are driven by the need to provide symptomatic relief for a specific patient population (Results stratified by prescriber specialty not shown due to RIDOH's Small Numbers Policy). The prescriber report is available to providers who prescribed a controlled substance within the previous six months. Providers that rarely prescribe controlled substances may not find value in this report.

While it is promising that many respondents have viewed the report, about 20% of respondents still have not or have not regularly viewed the report. Due to the frequency that the report is sent out, it is unlikely that a prescriber will view the report every quarter, and a prescriber may not have to view the report for them to determine if it is useful or meaningful in their practice. This is especially true among the inpatient respondents, as they are likely not seeing the same patient population over multiple visits, and trends in their prescribing may not be as relevant to them as it would be to outpatient respondents.

Though a small proportion of respondents reported changing their prescribing habits after viewing the report, this does not directly speak to the usefulness of the report. The prescriber report is designed to be a tool to increase provider awareness of their prescribing habits and gauge where these patterns are in relation to their peers. If a provider feels confident with their prescribing habits, a change in practice after viewing the report may not be necessary.

Though the responses from respondents that were unfamiliar with the report were not included in this analysis, the majority of excluded responses were largely from emergency medicine/urgent care prescribers. In addition to this, excluded respondents report "lack of knowledge of report", "difficulty finding report", and "technical difficulties" as barriers to viewing the report (Results not shown due to due to RIDOH's Small Numbers Policy and exclusion from analysis). This highlights the need for increased communication and training around the utilization of the prescriber report.

A limitation of this analysis is that the results from this survey are not generalizable, as they pertain to the experiences of prescribers practicing in RI and using the specific PDMP system procured by the state. Due to the voluntary nature of the survey, prescribers were not required to respond to any or all questions, which lead to a low response rate (~4%). A low response rate, however, is expected for this survey as it was presented to professionals without a direct incentive. Time constraint was reported as a barrier to viewing the prescriber report and may have been a barrier for professionals to complete the survey. In addition, as with many survey results, response bias might influence a respondent's answers and lead to flawed conclusions. We were also

unable to stratify by meaningful groups, such as prescriber specialty, due to low response counts in some categories.

Future work will focus on further evaluating the usefulness of the prescriber report and ensuring that utilization and general communication regarding the report is improved to allow all interested providers an opportunity to easily access it and understand its purpose as a tool. In addition to this, efforts will increase future survey completion as responses to these surveys will be used to make the prescriber report more valuable to RI prescribers.

References

1. Rhode Island Department of Health. Prescription Drug Monitoring Program (PDMP) [Online]. https://health.ri.gov/medicine-and-drugs/prescription-drug-monitoring-program-pdmp
2. Rhode Island Department of Health. Rhode Island Small Numbers Reporting Policy [Online]. https://health.ri.gov/sites/g/files/xkgbur1006/files/2025-02/SmallNumbersReporting.pdf

Authors

Taylor J. Mello, MPH, is the Senior Prescription Drug Monitoring (PDMP) Epidemiologist at RIDOH.

Adam Z. Nitenson, PhD, PDMP, is the Health Research Project Director at RIDOH.

Jane Fernandez, PharmD, is the Consultant PDMP Pharmacist at RIDOH.

Disclosures

None

Correspondence

Taylor Mello, MPH

Taylor.Mello@health.ri.gov

Rhode Island Monthly Vital Statistics Report
Provisional Occurrence Data from the Division of Vital Records

VITAL EVENTS	REPORTING PERIOD		
	NOVEMBER 2024	12 MONTHS ENDING WITH NOVEMBER 2024	
	Number	Number	Rates
Live Births	837	10,874	10.3*
Deaths	839	10,713	10.1*
Infant Deaths	2	37	3.4#
Neonatal Deaths	1	28	2.6#
Marriages	527	6,617	6.2*
Divorces	188	2,536	2.4*

* Rates per 1,000 estimated population
# Rates per 1,000 live births

Underlying Cause of Death Category	REPORTING PERIOD			
	MAY 2024	12 MONTHS ENDING WITH MAY 2024		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	260	2,376	216.5	2,827.5
Malignant Neoplasms	165	2,211	201.5	4,341.5
Cerebrovascular Disease	31	434	39.5	637.0
Injuries (Accident/Suicide/Homicide)	86	962	87.7	11,653.0
COPD	40	465	42.4	392.5

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.
(b) Rates per 100,000 estimated population of 1,097,379 for 2020 (www.census.gov)
(c) Years of Potential Life Lost (YPLL).

NOTE: Totals represent vital events, which occurred in Rhode Island for the reporting periods listed above.
Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

SAVE THE DATE

RHODE ISLAND MEDICAL SOCIETY

CONVIVIUM

213TH ANNUAL MEETING & AWARDS DINNER

SEPTEMBER 25, 2025
THE SQUANTUM ASSOCIATION

6:00 PM RECEPTION
7:00 PM DINNER

FOR MORE INFO VISIT
RIMEDICALSOCIETY.ORG

YOUR VOICE.
YOUR PATIENTS.
YOUR PROFESSION.

RIMS gratefully acknowledges the practices who participate in our discounted Group Membership Program

ANCHOR MEDICAL ASSOCIATES

BROWN EMERGENCY MEDICINE
BROWN PHYSICIANS, INC.

BROWN MEDICINE
BROWN PHYSICIANS, INC.

BROWN SURGICAL ASSOCIATES
BROWN PHYSICIANS, INC.

COASTAL MEDICAL

CCAP
COMPREHENSIVE COMMUNITY ACTION PROGRAM
YOUR COMMUNITY'S HELPING HAND

east bay community action program
THE BRIDGE to SELF-RELIANCE

SKIN PROS

Thundermist!
HEALTH CENTER

UNIVERSITY ORTHOPEDICS
Healers. Innovators. Teachers.

University Otolaryngology

WellOne
Primary Medical and Dental Care

Wood River
Health Services
The Heart of South County since 1976

For more information about group rates, please contact Ali Walz, RIMS Director of Member Services

CDC's Advisory Committee on Immunization Practices' meeting held June 25–26

Approves RSV antibody treatment, influenza shots without thimerosal

MARY KORR
MANAGING EDITOR

ATLANTA, GA — The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) met June 25–26, 2025, at CDC headquarters in Atlanta. It was the first formal meeting for the newly constituted group, after the dismissal of its former 17 members by the Secretary of Health and Human Services, **ROBERT F. KENNEDY, JR.** He replaced them with eight new members, named on Kennedy's X feed. One recently dropped out during a financial review, leaving the current group at seven members.

Dr. Martin Kulldorff shown during the June 26th ACIP meeting. [RIMJ]

At the first meeting on June 25th, which was open to the media and the general public through an online YouTube feed and which RIMJ attended, the ACIP announced it would form new work groups. They would study and evaluate the cumulative effects of the childhood and adolescent vaccine schedules, the hepatitis B vaccine dose given at birth, and the combination measles, mumps, rubella (MMR) and chickenpox vaccine, said chair **DR. MARTIN KULLDORFF**. He is a biostatistician and epidemiologist formerly at Harvard Medical School who has served on the Food and Drug Administration's Drug Safety and Risk Management Advisory Committee and the CDC's ACIP Vaccine Safety Subgroup.

A second new work group will look at vaccines that haven't been reviewed in more than seven years, Dr. Kulldorff said, including whether the hepatitis B vaccine should be universally recommended for newborns.

CDC staff also presented data on COVID-19 vaccines, showing their safety and efficacy in reducing hospitalizations and deaths. The numbers presented for the 2024 to present season were: 79 percent effectiveness for ages nine months to four-years-old; 57 percent for ages between five and 17-year-olds; and 34 percent for those over 18. Risks discussed included myocarditis and pericarditis.

RSV approved

On the second day of the meeting, in a somewhat surprise move to outside public health experts, the ACIP voted to recommend Clesrovimab that protects infants against respiratory syncytial virus (RSV). The monoclonal antibody created by Merck is recommended for use in infants younger than eight months born during or entering their first RSV season. In a second vote, it was approved to update the resolution for the federal Vaccines for Children program to include information about the newly approved shot. The vote was 7–0.

Merck's shot is the second RSV monoclonal antibody of its kind on the market. The first, a shot from Sanofi and AstraZeneca called Beyfortus, was approved by the Food and Drug Administration (FDA) in July 2023 and prevents RSV lower respiratory tract disease in infants entering or during their first RSV season.

Pregnant women also have access to Pfizer's RSV vaccine Abrysvo, which is recommended to protect newborns from lower respiratory infections. The shot is approved for use during the 32nd and 26th weeks of pregnancy during the RSV season, which typically starts in September and runs through January in the United States.

Thimerosal discussion

A vote was also taken on removing thimerosal, used as a preservative, from the seasonal influenza vaccine. In 2001, the organomercury compound was removed by the FDA from children's vaccines, and which has been phased out of other vaccines.

Currently it is present in four to five percent of multi-vial influenza vaccines. The committee voted against recommending vaccines that include the preservative for both children and adults. The votes for the different age groups were five yes, one no, one abstention.

Concern was raised by participants about limiting the availability of vaccines in multi-dose vials, already approved and on the schedule, and suggestions for investigating other preservatives down the line.

Influenza vaccines for upcoming season

The following recommendations were presented to the ACIP:

U.S. Influenza Vaccine Composition for the 2025–2026 Influenza Season

- All influenza vaccines marketed in the United States for the 2025–2026 season will be trivalent
- U.S. influenza vaccine composition for 2025–2026 includes an update to the influenza A(H3Nz) component:
  - An A/Victoria/4897/2022 (H1N1)pdmog-like virus for egg-based vaccines or an A/Wisconsin/67/2022 (H1N1) pdmog-like virus for cell-based and recombinant vaccines;
  - An A/Croatia/10136RV/2023 (H3Nz)-like virus for egg-based vaccines or an A/District of Columbia/27/2023 (H3N2)-like virus for cell-based and recombinant vaccines;
  - A B/Austria/1359417/2021 (B/Victoria lineage)-like virus

Approval of Flublok (RIV3) for Persons Aged 9 through 17 Years

- Approved by FDA in March 2025
- Previously approved for ≥18 years; new age indication is ≥9 years
- Information has been updated in the Table of vaccines for 2025–2026

FluMist (LAIV3) for Self- or Caregiver Administration

- Approved by FDA in September 2024; presented to ACIP in April 2025
- Anticipated to be available for the 2025–2026 influenza season
- Consumers will be able to order FluMist for delivery for eligible recipients
- Screening for eligibility performed by online pharmacy, based on ACIP criteria
- Approved for self-administration for persons aged 18 through 49 years, or by caregiver aged ≥18 years for recipients aged 2 through 17 years
- LAIV will continue to be available for administration by healthcare providers as previously. No changes made to recommendations regarding appropriate populations, contraindications, or precautions.

Dr. Kulldorff concluded the meeting by stating the ACIP would use "evidence-based medicine and scientific research in an unbiased and transparent way," as it moves forward.

The Committee's recommendations are forwarded to CDC's Director and once adopted become official CDC policy. These recommendations are then published in CDC's *Morbidity and Mortality Weekly Report* (*MMWR*).

The slide shows from the two-day meeting and resolutions approved are available at https://www.cdc.gov/acip/meetings/presentation-slides-june-25-26-2025.html ❖

AMA, 78 Medical societies issue open letter backing vaccination to protect against respiratory viruses

CHICAGO – With respiratory viruses expected to surge this fall, the American Medical Association (AMA) and 78 leading medical societies [including the Rhode Island Medical Society], reaffirm their support for vaccination as the best way to protect against the flu, COVID-19, and RSV and their potentially serious complications. The organizations call on partners – insurers, hospitals, and public health agencies – to ensure these life-saving vaccines remain available to patients without cost sharing.

An open letter to the American people:

With the severe influenza season the U.S. experienced during the 2024–2025 respiratory virus season, and the recognition that we will likely see another surge in respiratory viruses this fall, we know strong physician leadership is essential to reducing preventable illness, hospitalizations, and death. Vaccines for influenza, RSV, and COVID-19 remain among the best tools to protect the public against these illnesses and their potentially serious complications – and physicians are among the most trusted voices to recommend them. We come together as physicians from every corner of medicine to reaffirm our commitment to these lifesaving vaccines.

Recent changes to federal immunization review processes raised concerns across the medical and public health community. In this moment of uncertainty, physicians must align around clear, evidence-based guidance for patients.

We commit to working together to promote public understanding and confidence in the use of vaccines to avoid another severe respiratory virus season and resurgence of vaccine-preventable illnesses and deaths. We call on our partners – from insurers to hospitals to public health agencies – to ensure vaccines remain available to patients without cost sharing.

The health and safety of the public remains our top priority, and we will continue to support evidence-based immunizations to help prevent severe disease and protect public health. ❖

Rhode Island sees decrease in drug overdose deaths, continues a two-year decline

PROVIDENCE — Governor **DAN McKEE** and the Governor's Overdose Task Force announced on June 12th that overdose deaths in Rhode Island dropped 25% since 2022 – continuing a two-year decline and falling to levels not seen since before the COVID-19 pandemic.

According to the newly released data from the Rhode Island Department of Health (RIDOH) Substance Use Epidemiology Program, 329 people lost their lives to accidental overdoses during 2024. This is an 18.6% decrease in overdose deaths compared to 2023.

These data indicate that Rhode Island is showing notable progress in its 2030 Action Plan goal to reduce overdose deaths by 30%.

The Governor's Overdose Task Force focuses on four key areas guided by the State's Strategic Plan: Prevention, Rescue and Harm Reduction, Treatment, and Recovery. This work is centered in racial equity, ensuring that diverse community voices are heard and valued in decision-making processes. Additionally, the Task Force combines data-driven insights and community engagement to connect Rhode Islanders to local resources.

"At the heart of this work is our deep commitment to addressing the stigma that prevents individuals and families from accessing lifesaving resources," said Governor's Overdose Task Force Director **CATHY SCHULTZ**. "The Task Force and its nine work groups continue to normalize conversations about substance use disorder and overdose. That is what it will take to help end this crisis."

"The fact that we are still losing people tells us that we still have much work to do," said **RICHARD LeCLERC**, Director of the Department of Behavioral Healthcare, Developmental Disabilities & Hospitals. "That means all of us have to continue to work together strategically to help people understand that overdose deaths are preventable, that help and care are available, that people can and do recover from substance use disorders."

"Every single overdose death is preventable. Recovery is within reach for every person living with the disease of addiction," said Director of Health **JERRY LARKIN, MD**. "We need to keep coming together as families, as communities, and as a state to build on this momentum and continue reducing the number of drug overdose deaths in Rhode Island."

Overview of 2024 Rhode Island Fatal Overdose Data

Fatal drug overdose data in Rhode Island are collected by the Office of the State Medical Examiners and State Health Laboratories. Because many cases require complex drug testing, it can take several months to complete and confirm yearly overdose data.

These data show:

- Most people who died from a drug overdose were male (70%), similar to previous years.
- In 2024, individuals age 45 to 54 experienced the highest burden of overdose (59.3 per 100,000 residents), followed by those age 55 to 64 (55.6 per 100,000 residents).
- The rate of fatal overdose decreased among all age groups except for Rhode Islanders age 55 to 64.
- In 2024, the rate of fatal overdoses decreased among all race and ethnicity groups in Rhode Island.
- Non-Hispanic, Black Rhode Islanders still experience the highest burden of fatal overdose followed by non-Hispanic, white Rhode Islanders, and Hispanic or Latino Rhode Islanders.
- Opioids and fentanyl continue to drive the overdose epidemic in Rhode Island.
- In 2024, 69% of overdose deaths involved any opioid (including fentanyl), while 57% involved fentanyl specifically.
- The total number of opioid-involved fatal overdoses in 2024 decreased by 36% compared to 2022.
- Cocaine-involved overdose deaths surpassed fentanyl-involved overdose deaths for the first time since 2013, with 6 in 10 (61%) involving cocaine.
- In most of these cases, another substance was also present with cocaine in an individual's system according to toxicology reports.
- Eight in 10 overdose deaths took place in private settings like homes.
- The municipalities with the highest rates of fatal overdoses were Woonsocket (58.1 overdose deaths per 100,000 residents); Providence (45.4 per 100,000 residents); Pawtucket (33.3 per 100,000 residents); Cranston (25.5 per 100,000 residents); and Warwick (21.7 per 100,000 residents). Please note: Rates are calculated only for municipalities with 15 or more fatal overdoses occurring in 2024. ❖

Governor McKee, EOHHS award $6.7M in grants to bolster primary care

PROVIDENCE — Governor **DAN McKEE** and his Executive Office of Health and Human Services (EOHHS) announced $6.7 million in grants awarded to support 85 primary care practices across Rhode Island.

Primary care providers were invited to apply for grants across three tiers, representing different criteria:

- **Tier 1:** Primary care practices agree to and demonstrate that they have accepted new patients onto their patient panel.
- **Tier 2:** The primary care practices will recruit new primary care physicians or mid-level providers, such as Nurse Practitioners or Physician Assistants, to the Rhode Island primary care workforce.
- **Tier 3:** Primary care provider and/or practice that enrolls as a new Medicaid Provider in the Rhode Island Medicaid program.

Tier 1 and Tier 2 awards are listed in the link to a chart below. Providers who applied for a grant through Tier 3 – enrolling as a new Medicaid partner – will only be notified if they are awarded funding upon their successful enrollment in Medicaid on or before September 1, 2025. To learn more about the award recipients: https://eohhs.ri.gov/sites/g/files/xkgbur226/files/2025-06/Primary%20Care%20Grant%20Recipients%2006.18.25%20%281%29.pdf

"Primary care is the foundation of preventive care and overall positive health outcomes," said EOHHS Secretary **RICHARD CHAREST**. "These grants will support 85 primary care practices in Rhode Island to expand their practices so they can see more patients, which, in turn, will ease the burden on Rhode Islanders seeking access to primary care."

"The mission of Rhode Island's Medicaid program, which provides coverage to one in three Rhode Islanders, is to improve access to care for our state's most vulnerable communities," said Rhode Island Medicaid Director **KRISTIN PONO SOUSA**. "We understand that even when people have access to health insurance, they still experience barriers to care. By providing funds to bolster primary care in our state, RI Medicaid is reinforcing our commitment to ensuring every family in Rhode Island can live a healthy life."

In addition to this grant opportunity, Governor McKee, joined by members of his State Health Care System Planning Cabinet, recently announced the following strategic actions to strengthen Rhode Island's primary care system:

- Accelerating the Medicaid rate review for primary care
- Requiring commercial health insurers to increase primary care funding
- Easing prior authorization requirements
- Expanding the primary care student loan forgiveness program

Rhode Island, like many other states, has seen a continuing decline in the primary care workforce in recent years; primary care providers are retiring, and the pipeline to replace them is limited. ❖

RIDOH launches campaign to spotlight men's mental health

PROVIDENCE — The Rhode Island Department of Health (RIDOH) has launched You Good, Man?, a statewide campaign to raise awareness and prevent suicide among working-age men — a population experiencing suicide at nearly twice the rate of the general public in Rhode Island.

"Society often focuses on the physical health of men – be it fitness, or annual checkups, or heart health. But mental health and well-being is just as important," said Director of Health **JERRY LARKIN, MD**. "This campaign is about creating a culture where men and boys feel comfortable reaching out and checking in on their friends and coworkers. No one should struggle in silence."

The You Good, Man? campaign features a powerful, locally produced video and a three-month media buy across social media, digital and streaming platforms, local movie theaters, and gas stations. As part of the campaign, YouGoodMan.org was created as a resource hub offering mental health tips, warning signs, conversation guides, and local support services.

The goal is to normalize conversations about mental health, empower friends, coworkers, and loved ones to check in, and encourage men to accept help when it's offered.

According to the 2023 Rhode Island Behavioral Risk Factor Surveillance System (BRFSS) survey, 11% of men said they usually or always feel lonely. Suicide death rates in Rhode Island are highest among working-age males (25–64 years old). The death rate for this group is more than twice as high as Rhode Island's overall suicide death rate. Working-aged men reported not having adequate social support in comparison to females in the same age group. According to 2024 Rhode Island fatal overdose data, the majority of individuals who died from a drug overdose – 70 percent – were male.

In addition to their impacts on mental health, loneliness and social isolation significantly impact physical health. They are associated with increased risk for heart disease, stroke, dementia, and type 2 diabetes.

For more information on the program, go to https://preventsuicideri.org/get-help/you-good-man ❖

Andrew Green, MD, first in New England to use ARVIS® augmented reality system for joint replacement surgery

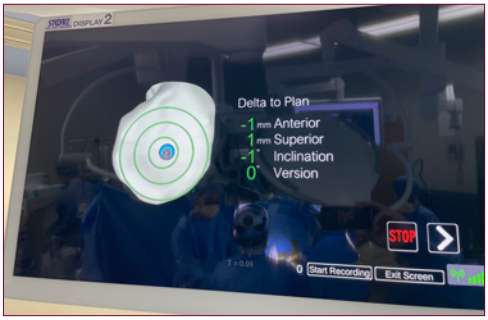
EAST PROVIDENCE — **ANDREW GREEN, MD**, a renowned shoulder specialist with University Orthopedics, recently became the first surgeon in New England to utilize ARVIS®, a groundbreaking augmented reality (AR) guidance system for shoulder joint replacement surgery.

Developed by Enovis™, ARVIS® (Augmented Reality Visualization and Information System) is the only AR platform currently available in the United States that enables surgical navigation for shoulder joint replacements, all within a single, compact system, thus facilitating precise implant placement.

ARVIS® integrates tracking cameras, a 3D AR display, and a hands-free interface within a surgical helmet-compatible eyepiece, as shown here by **Dr. Andrew Green** of University Orthopedics.
[PHOTOS: UNIVERSITY ORTHOPEDICS]

ARVIS® integrates tracking cameras, a 3D AR display, and a hands-free interface within a surgical helmet-compatible eyepiece. Its proprietary hardware enhances surgical precision while minimizing the physical footprint and financial burden associated with traditional robotic systems.

"I've incorporated ARVIS® into my practice because it's designed specifically to fit the needs of my shoulder patients," said Dr. Green, Chief of Shoulder and Elbow Surgery at Brown University Health and University Orthopedics. "After more than 30 years performing shoulder replacements, I know how important the small details are to a good result. My patients deserve the best tools and technology available. The ARVIS® system helps me to precisely position the implants, which is especially important in cases with more severe bone deformity. Published research studies show that computer-assisted planning and navigation improve the surgical accuracy over traditional unguided surgical techniques. With ARVIS®, I have complete control of the surgery." ❖



Roger Williams Medical Center's Blood and Marrow Transplant program introduces new CAR T-cell therapies

PROVIDENCE — Roger Williams Medical Center's Blood and Marrow Transplant and Cellular Therapy (BMT) program announced that KITE Pharmaceutical's Chimeric Antigen Receptor T-cell (CAR T-cell) therapies for the treatment of certain blood cancers, Yescarta and Tecartus, are now available in Rhode Island.

Yescarta is indicated for the treatment of two types of adult non-Hodgkin lymphoma: 1. relapsed or refractory large B-cell lymphoma, and 2. relapsed or refractory follicular lymphoma. Tecartus is indicated for the treatment of adults with mantle cell lymphoma or acute lymphoblastic leukemia.

RITESH RATHORE, MD, Director of Hematology/Oncology and Acting Director of the Roger Williams Bone Marrow program, said, "We are excited about this partnership which enables us to provide patients with life-threatening blood cancers with a treatment option that can be lifesaving, all within their home state and without having to worry about leaving the vicinity of their home and loved ones."

In 2020, the BMT program added the Novartis Pharmaceuticals CAR T-cell therapy product, Kymriah, to its available treatment regimens. While Kymriah treats similar cancers as those treated by the KITE products, it is important to note that different products indicated for the same cancer treatments are not created equally. Some may work better for some than others, and having multiple options to discuss with healthcare providers is a huge benefit to patients and the success of their treatment.

The BMT program, celebrating its 30th year of caring, is dedicated to providing Rhode Island and nearby residents suffering from difficult cancer diagnoses with the most current and effective treatments available. The program is currently working with another pharmaceutical company to include CAR T-cell therapy for multiple myeloma to the available treatment regimens within the next year. ❖

Medicare Trustees warn about access to care for seniors

CHICAGO – Medicare Trustees warned that long-term access to care for seniors is threatened by Medicare's failure to keep up with the cost of practicing medicine, adding to the drumbeat of similar warnings from policymakers and the American Medical Association (AMA).

The Medicare Trustees report pointed out that rising costs are outpacing physician payments. As a result, physician practices are struggling to stay open. "Absent a change in the delivery system or level of update by subsequent legislation, the Trustees expect access to Medicare-participating physicians to become a significant issue in the long term," the report said.

"Medicare Trustees join the Medicare Payment Advisory Commission, members of Congress, medical organizations and, most importantly, patients in recognizing that this issue is affecting physician practices today. As physicians, we are trained to spot trends, but you don't have to have a medical degree to see this one. While we are grateful for the growing consensus, the problem does not go away by merely recognizing it. Medicare reform must be the next step, and we must do it now," said AMA President **BOBBY MUKKAMALA, MD**.

As one of the few Medicare providers without an inflationary payment update, physicians have watched their payments (when adjusted for inflation in practice costs) decline 33% from 2001 to 2025. This year, Medicare cut payments by another 2.8 percent. These increasingly thin operating margins disproportionately affect small, independent, and rural physician practices, as well as those treating low-income or underserved communities.

The House recently passed an update for 2026 that substantially accounts for inflation and is an important step toward Medicare reform. The AMA is working to include that provision in the Senate and the final version of the reconciliation bill.

The report warned of a two-tiered medical system with the "quality of health care received by Medicare beneficiaries will, under current law, fall over time compared to that received by those with private health insurance."

Added Dr. Mukkamala, "Medicare Trustees have clearly explained the problem: Physicians are facing high medical inflation and lowered payments. This year's 2.8 percent cut is a painful – and ongoing – reminder that the Medicare payment system needs reform. We look forward to advancing many of our thoughts as we work on this issue with Congress and the administration in the coming year."

The report can be found here. ❖

Brown joins amicus brief detailing how federal research cuts imperil America's global competitiveness

PROVIDENCE [BROWN UNIVERSITY] — Brown University along with 23 other colleges and universities filed an amicus brief on June 9th in support of Harvard University's motion for summary judgment in a lawsuit challenging the federal government's funding freeze on approximately $3 billion in research grants and contracts to the university.

The amicus brief urged the federal court hearing the case to sustain federal investments in scientific research at U.S. universities, arguing that protecting research is in the public interest and that compromising funding would come with irreparable harm. The brief emphasized that for more than 80 years, the federal government has invested heavily in scientific research at U.S. universities, enabling breakthroughs that save and improve lives and build economies.

"This funding has fueled American leadership at home and abroad, yielding radar technology that helped defeat the Nazis, computer systems that put humans on the Moon, and a vaccine that saved millions during a global pandemic," the brief states. "Many of these life-changing and history-altering innovations came out of work that had an entirely different initial focus."

The amicus brief argued that the U.S. has long advanced scientific research in collaboration with universities, and the result has been a symbiotic partnership that has made America a global leader.

"The government identifies projects that are vital to the national interest," the brief notes. "Agencies award funding for those initiatives, usually on a competitive basis, selecting recipients based on scientific merit and their ability to create value for the American people. And in exchange, the country's top scientists harness federal resources to drive gains in fields from nuclear power to biomedicine to artificial intelligence.

The universities argued that broad cuts to federal research funding, like those Harvard is challenging in court, disrupt projects, ruin experiments and datasets, and destroy the careers of aspiring scientists. Funding cuts also deter investment in the long-term research that only institutions with federal funding can pursue, threatening the pace of progress and undermining American leadership.

"Terminating funding to universities jeopardizes American innovation and economic growth by severely limiting their ability to play their vital, longstanding roles in expanding scientific knowledge," the brief states. "These cuts to research funding risk a future where the next pathbreaking innovation – whether it is a cure for cancer or Alzheimer's, a military technology, or the next Internet – is discovered beyond our shores, if at all."

The brief noted that sustained government-university collaboration has contributed to inventions and breakthroughs ranging from nuclear reactors and national security measures to

cancer treatments, DNA sequencing technology and hurricane forecasting techniques.

The amicus brief urged the court to grant summary judgment to Harvard in its lawsuit against the government, which would allow the judge to rule on the case without a full trial. Even schools that do not experience direct funding cuts will suffer, it argued – scientists work across institutions, grants issued to one university support researchers from others schools, and cutting-edge research is often conducted via collaboration.

"Extensive cuts to federal research funding to universities threaten much of what has made the U.S. research enterprise a juggernaut of growth and prosperity," the brief states.

In addition to Brown, the brief's signatories include American University; Boston University; California Institute of Technology; Colorado State University; Dartmouth College; Georgetown University; Johns Hopkins University; Massachusetts Institute of Technology; Michigan State University; Oregon State University; Princeton University; Rice University; Rutgers University; Stanford University; Tufts University; University of Delaware; University of Denver; University of Maryland, Baltimore; University of Maryland, College Park; University of Oregon; University of Pennsylvania; University of Pittsburgh; and Yale University. ❖

The Miriam Hospital opens 75-year-old time capsule, kicking off major modernization project

PROVIDENCE — In a moving celebration of history and progress, The Miriam Hospital on June 19th opened a time capsule that had been sealed in the cornerstone of its second building – formerly the Jewish Orphanage of Rhode Island – nearly 75 years ago. The capsule was originally placed in 1950 by then hospital president Benjamin Brier.

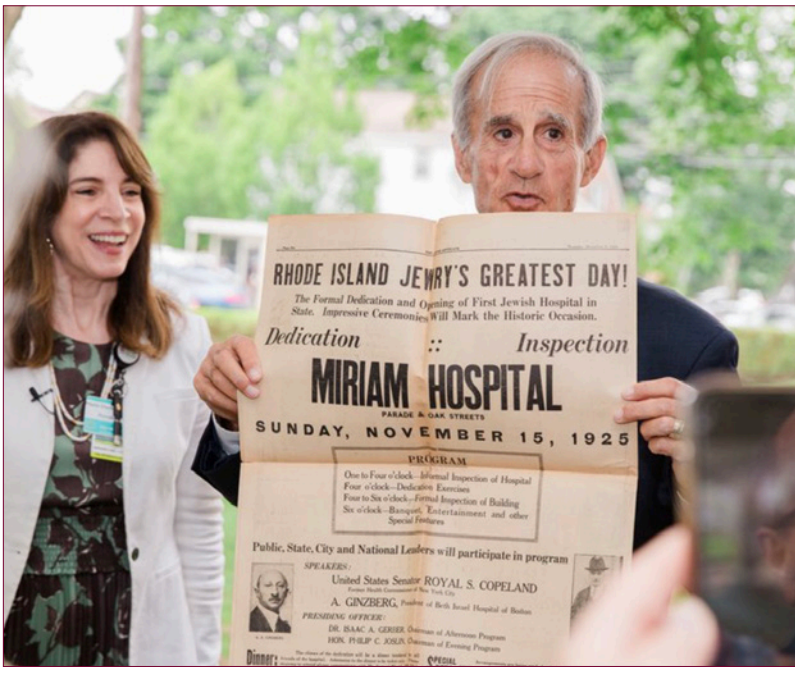
Marking a once-in-a-lifetime moment for the hospital and the broader community, the event welcomed dozens of staff, supporters, and special guests to the hospital's lawn to witness the unveiling.

"When my grandfather placed this time capsule in the cornerstone 75 years ago, I doubt he imagined that one of his grandchildren would one day return to open it. Today is not just a celebration of the past, it's a continuation of a legacy rooted in community, service, and care," said **JEFFREY G. BRIER**, former chairman, The Miriam Hospital Board of Trustees.

Inside the time capsule were numerous artifacts, including:

- A bundle of letters of support, including one from then-Rhode Island Governor Dennis J. Roberts
- A Sunday edition of the *Providence Journal*
- A 1925 copy of the *Jewish Advocate* newspaper, specially dedicated to the Parade Street Hospital dedication
- Original ceremony program
- Several newly minted 1951 dimes and more!

"These items are more than just a reminder of our past, they are a testament to the enduring values of compassion, resilience, and community that continue to define The Miriam Hospital today," said Hospital President **MARIA DUCHARME, DNP, RN**. "We honor the legacy of those who built and cared for patients in this hospital as we begin The Miriam Hospital's next phase – a bold reimagining of how we deliver care, grounded in our history and shaped by the very people who live it every day, our dedicated clinicians and staff."



A time capsule unsealed at The Miriam Hospital on June 19, 2025 revealed a 100-year-old newspaper celebrating the hospital's founding. Unveiling the contents was **Jeffrey G. Brier**, former chairman of The Miriam Hospital (2004–2008), who joined Hospital President **Maria Ducharme, DNP, RN**. [COURTESY OF THE MIRIAM HOSPITAL]

The event also marked the official start of the hospital's long-anticipated building replacement project, with the removal of the historic cornerstone serving as both a symbolic and physical first step. ❖

HHS, CMS hold roundtable on prior authorizations

WASHINGTON, DC — U.S. Health and Human Services (HHS) Secretary **ROBERT F. KENNEDY, Jr.** and Centers for Medicare & Medicaid Services (CMS) Administrator **DR. MEHMET OZ** met on June 23rd with industry leaders to discuss their efforts to streamline and improve the prior authorization processes for Medicare Advantage, Medicaid Managed Care, Health Insurance Marketplace® and commercial plans covering nearly eight out of 10 Americans.

In a roundtable discussion hosted by HHS, health insurers pledged six key reforms aimed at cutting red tape, accelerating care decisions, and enhancing transparency for patients and providers. Companies represented at the roundtable included Aetna, Inc., AHIP, Blue Cross Blue Shield Association, CareFirst BlueCross BlueShield, Centene Corporation, The Cigna Group, Elevance Health, GuideWell, Highmark Health, Humana, Inc., Kaiser Permanente, and UnitedHealthcare.

Participating health insurers have pledged to:

- Standardize electronic prior authorization submissions using Fast Healthcare Interoperability Resources (FHIR®)-based application programming interfaces.
- Reduce the volume of medical services subject to prior authorization by January 1, 2026.
- Honor existing authorizations during insurance transitions to ensure continuity of care.
- Enhance transparency and communication around authorization decisions and appeals.
- Expand real-time responses to minimize delays in care with real-time approvals for most requests by 2027.
- Ensure medical professionals review all clinical denials. ❖

Health insurance plans announce commitments to streamline, simplify and reduce prior authorization

WASHINGTON, DC – Health insurance plans on June 23rd announced a series of commitments to streamline, simplify and reduce prior authorization – a critical safeguard to ensure their members' care is safe, effective, evidence-based and affordable. Building on health plans' existing efforts, these new actions are focused on connecting patients more quickly to the care they need while minimizing administrative burdens on providers.

These commitments are being implemented across insurance markets, including for those with commercial coverage, Medicare Advantage and Medicaid-managed care consistent with state and federal regulations, and will benefit 257 million Americans.

For patients, these commitments will result in faster, more direct access to appropriate treatments and medical services with fewer challenges navigating the health system. For providers, these commitments will streamline prior authorization workflows, allowing for a more efficient and transparent process overall, while ensuring evidence-based care for their patients.

"The health care system remains fragmented and burdened by outdated manual processes, resulting in frustration for patients and providers alike. Health plans are making voluntary commitments to deliver a more seamless patient experience and enable providers to focus on patient care, while also helping to modernize the system," said AHIP President and CEO **MIKE TUFFIN**.

"These measurable commitments – addressing improvements like timeliness, scope and streamlining – mark a meaningful step forward in our work together to create a better system of health," said **KIM KECK**, President and CEO, Blue Cross Blue Shield Association. "This is an important foundation to address bigger problems together, at a time when technology and interoperability can deliver real improvements to patient experience."

Participating health plans commit to:

- **Standardizing Electronic Prior Authorization:** Participating health plans will work toward implementing common, transparent submissions for electronic prior authorization. This commitment includes the development of standardized data and submission requirements (using FHIR® APIs) that will support seamless, streamlined processes and faster turn-around times. The goal is for the new framework to be operational and available to plans and providers by January 1, 2027.
- **Reducing the Scope of Claims Subject to Prior Authorization:** Individual plans will commit to specific reductions to medical prior authorization as appropriate for the local market each plan serves, with demonstrated reductions by January 1, 2026.
- **Ensuring Continuity of Care When Patients Change Plans:** Beginning January 1, 2026, when a patient changes insurance companies during a course of treatment, the new plan will honor existing prior authorizations for benefit-equivalent in-network services as part of a 90-day transition period. This action is designed to help patients avoid delays and maintain continuity of care during insurance transitions.
- **Enhancing Communication and Transparency on Determinations:** Health plans will provide clear, easy-to-understand explanations of prior authorization determinations, including support for appeals and guidance on next steps. These changes will be operational for fully insured and commercial coverage

by January 1, 2026, with a focus on supporting regulatory changes for expansion to additional coverage types.

- **Expanding Real-Time Responses:** In 2027, at least 80 percent of electronic prior authorization approvals (with all needed clinical documentation) will be answered in real-time. This commitment includes adoption of FHIR® APIs across all markets to further accelerate real-time responses.
- **Ensuring Medical Review of Non-Approved Requests:** Participating health plans affirm that all non-approved requests based on clinical reasons will continue to be reviewed by medical professionals – a standard already in place. This commitment is in effect now.

"Private-sector collaboration and solution-oriented commitments are critical to improve policy and tackle challenges. With membership spanning the entire healthcare continuum, we appreciate the need to balance appropriate medical management with timely access to care. This announcement from health insurance plans is an important step toward improving the prior authorization process," said **MARIA GHAZAL**, President and CEO of the Healthcare Leadership Council. "We must seize this opportunity to turn these initiatives into real, sustained progress for patients."

"The National Health Council (NHC) welcomes the commitment of health plans to reform prior authorization practices as an encouraging step toward better access to care. For years, the NHC has called for changes that make the system work easier and better for people living with chronic diseases and disabilities," said **RANDALL RUTTA**, NHC's Chief Executive Officer. "The NHC is a ready partner to AHIP, BCBSA and health plans making these commitments to promote meaningful action that reduces administrative burden, increases transparency and centers on the needs of patients."

"We are encouraged by this collective commitment to reform prior authorization practices. Physicians have long advocated for reforms that help ensure that patients receive timely, medically necessary care and reduce administrative burden – including the elimination of unnecessary prior authorizations," said **SHAWN MARTIN**, Executive Vice President and Chief Executive Officer of the American Academy of Family Physicians. "While this commitment is a step in the right direction, we will ultimately measure its impact by real changes in the day-to-day experiences of patients and the physicians who care for them. We look forward to collaborating with payers to ensure these efforts lead to meaningful and lasting improvements in patient care."

Progress will be tracked and reported. A full list of participating health plans and additional information are available at: www.ahip.org/supportingpatients and https://www.bcbs.com/ImprovingPA. ❖

AMA responds as health insurers try again at voluntary prior authorization reforms

Credits agency officials & federal lawmakers for leadership and holding industry accountable

BOBBY MUKKAMALA, MD
PRESIDENT, AMERICAN MEDICAL ASSOCIATION

"The American Medical Association has been a leading voice in the call for prior authorization reform during the last decade, and we therefore applaud Secretary Kennedy, Administrator Oz, and Deputy Administrator Klomp for their leadership in convening the health insurance industry to address the urgent need for prior authorization reform. The proposals announced today would help right-size and streamline a process that is harming our patients daily. In fact, the announced reforms are ones the AMA has long advocated for to policymakers and echo commitments health plans previously agreed to in the 2018 Consensus Statement on Improving the Prior Authorization Process, including reducing the volume of prior authorization requirements, protecting care continuity as patients transition to new health plans, improving transparency, and automating the process.

"Despite widespread calls for meaningful reforms and the insurance industry's past promises, the prior authorization process remains costly, inefficient, opaque, and too often hazardous for patients. That is why the AMA enthusiastically supported recent federal regulations that applied reforms to limited health insurance markets, including Medicare Advantage. We are optimistic that health plans' pledge to expand the scope of several of these important reforms to other insurance types will provide more patients and physicians with relief. Moreover, we commend Senator Marshall and Congressman Murphy for their remarks at the event, as well as the continued bipartisan, bicameral commitment to codify these changes into law via passage of the Improving Seniors' Timely Access to Care Act.

"We are pleased with the industry's recognition that the current system is not working for patients, physicians or plans. However, patients and physicians will need specifics demonstrating that the latest insurer pledge will yield substantive actions to bring immediate and meaningful changes, break down unnecessary roadblocks, and keep medical decisions between patients and physicians. The AMA will closely monitor the implementation and impact of these changes as we continue to work with federal and state policymakers on legislative and regulatory solutions to reduce waste, improve efficiency, and, most importantly, protect patients from obstacles to medically necessary care." ❖

General Assembly approves bill to reduce prior authorization requirements for primary care

STATE HOUSE – The General Assembly today approved legislation sponsored by Senate Health and Human Services Committee Chairwoman **MELISSA MURRAY** and Rep. **BRANDON POTTER** to create a three-year pilot program prohibiting insurers from requiring prior authorization for medically necessary health care services ordered by patients' primary care providers.

The legislation (2025-S 0168B, 2025-H 5120A), which now goes to the governor, is meant to remove a roadblock that slows down patient care and consumes hours of primary care providers' and their staffs' time each day.

The bill is included the package of legislation endorsed by Senate leadership this session to address health care accessibility and affordability.

"It is the health care providers, not insurers, who know best what care is needed for their patients. And we need our primary care providers focused on providing care, not haggling with insurance companies," said Chairwoman Murray (D-Dist. 24, Woonsocket, North Smithfield).

Said Representative Potter (D-Dist. 16, Cranston), "We know all too well that Rhode Islanders are struggling to find primary care doctors, and those fortunate enough to have one are facing longer waits for appointments. The situation is only made worse when doctors have to spend their time battling insurance companies instead of treating patients. This is a step to ease that burden, expand access to basic health care, and ensure medical decisions are made by doctors based on what's best for patients – not by insurance companies prioritizing their bottom line."

The legislation would, for the three years beginning Oct. 1, prohibit insurers from imposing prior authorization requirements for any admission, item, service, treatment, or procedure ordered by a primary care provider, including general internists, family physicians, pediatricians, geriatricians, OB-GYNs, nurse practitioners, physician assistants and other health care providers who are credentialed with the insurer as a primary care provider. The prohibition does not extend to prescription drugs.

The bill requires annual reports from all insurers in Rhode Island, as well as from a workgroup from the Office of the Health Insurance Commissioner, to assist in assessing the success of the pilot program at improving access to primary care services, availability of staff to perform other office functions, increases in patient appointments and reductions in care delay.

If the pilot is found effective, it would be up to the General Assembly to vote to extend the program past its Oct. 1, 2028, expiration.

"Rhode Island's primary care system is at a breaking point. The recent closure of Anchor Medical left more than 25,000 patients searching for new primary care physicians – adding immense strain to a system already struggling to meet demand. Practices are reporting long wait times, limited capacity and increasing burnout. In this context, we must take immediate focused steps to strengthen the foundation of our health care system: primary care," said **KARA STAVROS, MD**, president of the Rhode Island Medical Society, in written testimony in favor of the legislation. "One of the most burdensome and unnecessary barriers to timely care is prior authorization. While intended as a cost-control measure, in practice, it delays needed treatment, increases administrative waste and undermines clinical decision-making.…In this moment of crisis, we cannot allow bureaucratic process to interfere with patients' ability to access timely, effective care. Rhode Islanders deserve better."

According to the American Medical Association, which has been advocating to reduce prior authorization requirements, the average physician practice completes 45 prior authorizations per physician per week. According to the most recent AMA survey, 94% of physicians believe prior authorization delays care. The Rhode Island Medical Society has also advocated for reductions in prior authorization requirements. ❖

Assembly OKs bill to help foreign-trained doctors to practice medicine in Rhode Island

STATE HOUSE — The General Assembly approved legislation introduced by Rep. **JOSEPH J. SOLOMON, Jr.** and Sen. **LORI URSO** that would help internationally trained physicians acquire medical licenses by eliminating barriers such as repeating residency programs.

The bill (2025-H 5108Aaa, 2025-S 0347Aaa) would allow internationally trained physicians to practice at health care facilities in Rhode Island under the guidance, assessment and evaluation of licensed physicians in the state, offering a pathway to full licensure outside of the current requirements to train in accredited United States residency training programs.

"Many talented foreign physicians face an assortment of bureaucratic hurdles in practicing medicine in America, including having to repeat residency, costly licensure requirements, and increasing restrictions," said Representative Solomon (D-Dist. 22, Warwick). "As the physician shortage worsens, we need to tap into this skilled pool of professionals to strengthen our medical community with multilingual, culturally competent physicians – especially in underserved communities."

This legislation is modeled on the Physician Pathway Act, which was enacted last year in Massachusetts after a statewide task force determined that more than one in five foreign-trained

health care professionals in the commonwealth were either unemployed or working in low wage, low-skilled jobs.

"We worked with the Department of Health and the Board of Medical Licensure to develop proper language to ensure due diligence in providing this pathway," said Senator Urso (D-Dist. 8, Pawtucket). "I hope it opens the door – even if just a little – to easing the burdens on our primary care physicians."

Under this legislation, an internationally-trained physician would be defined as "a physician who has received a degree of doctor of medicine or its equivalent from a medical school located outside the United States with recognized accreditation status from the Educational Commission for Foreign Medical Graduates."

Such physicians would be eligible to apply for a limited international physician license to practice medicine for a renewable one-year term after satisfying certain criteria, provided that such limited registration would supply a pathway to apply for the issuance of a full unrestricted license to practice medicine in accordance with the criteria.

The measure now moves to the governor's office. ❖

Katherine MacCallum, MD, of Brown Surgical Associates, Brown University Health, first in RI to perform Limb-Saving Limflow® TADV procedure

PROVIDENCE — In a major advancement for patients suffering from advanced peripheral arterial disease (PAD), **KATHERINE MACCALLUM, MD**, vascular surgeon with Brown Surgical Associates and Brown University Health, has become the first physician in Rhode Island to perform the LimFlow® TADV (Transcatheter Arterialization of the Deep Veins) procedure – a breakthrough treatment for patients with Chronic Limb-Threatening Ischemia (CLTI) who face the imminent threat of major amputation.

CLTI is a severe and life-altering form of PAD that manifests as non-healing wounds, intractable pain, and eventual limb loss.1 The LimFlow® TADV System is the first and only FDA-approved device designed to provide a minimally invasive solution by rerouting oxygenated blood into the deep venous system, restoring circulation where arteries have failed.

"This technology allows us to offer new hope to patients who previously had no other treatment options besides major amputation," said Dr. MacCallum. "By restoring blood flow to the foot, we're not only saving legs, we're enabling these patients to retain their independence, lessen the need for prolonged hospital and rehabilitation stays, and ultimately saving lives."

The LimFlow® procedure has been shown to significantly improve outcomes for patients with CTLI and no options for surgical bypass:

- 73% limb salvage at 12 months; 68% sustained at 24 months
- 92% healed or healing wounds at 12 months; 83% at 24 months
- 69% of patients pain-free at 24 months[2]

"LimFlow® TADV provides a new option for treating no-option CLTI with demonstrated limb salvage and wound healing through two years, even in the sickest patients," said **DR. DAN CLAIR**, as presented at VIVA 2024.3

The success of the LimFlow® procedure requires a collaborative team approach involving vascular surgeons, vascular lab technologists, wound care specialists, and podiatrists. Brown Surgical Associates and Brown University Health have long been at the forefront of such multidisciplinary models, and this new offering continues their tradition of innovation and comprehensive patient care. ❖

The success of the LimFlow® procedure requires a collaborative team approach involving vascular surgeons, vascular lab technologists, wound care specialists, and podiatrists. [COURTESY OF BROWN SURGICAL ASSOCIATES]

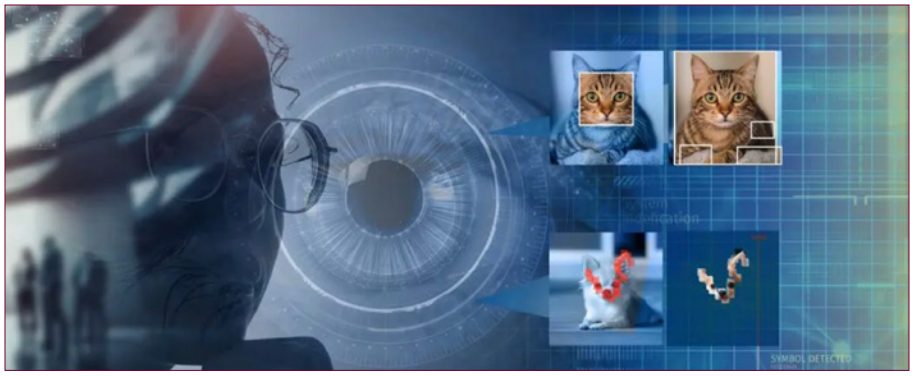
References

1. Centers for Disease Control and Prevention. Peripheral Arterial Disease (PAD).
2. LimFlow TADV Clinical Trial Data.
3. Clair D. VIVA 2024 Presentation.

Training AI to see more like humans

ALEXANDRIA, VA — Supported in part by the U.S. National Science Foundation, Brown University researchers are teaching AI to see more like humans, opening doors to more accurate AI solutions.

At Brown University, an innovative new project is revealing that teaching artificial intelligence to perceive things more like people may begin with something as simple as a game. The project invites participants to play an online game called Click Me, which helps AI models learn how people see and interpret images. While the game is fun and accessible, its purpose is more ambitious: to understand the root causes of AI errors and to systematically improve how AI systems represent the visual world.



The image compares how an AI model performs under two training conditions: with ClickMe maps and without them. On the left, "With ClickMe Maps", the model focuses on small, meaningful details – like the cat's facial features – mimicking how humans naturally interpret images. On the right, "Without Maps", the model pays attention to broader, less specific regions, such as the entire animal or background elements. [U.S. NATIONAL SCIENCE FOUNDATION, ADOBE STOCK BY METAMORWORKS. MANNA PATIPARNPRECHAVUT (RHODE ISLAND SCHOOL OF DESIGN) AND JAY GOPAL (BROWN UNIVERSITY)]

Over the past decade, AI systems have become more powerful and widely used, particularly in tasks like recognizing images. For example, these systems can identify animals, objects or diagnose medical conditions from images. However, they sometimes make mistakes that humans rarely do. For instance, an AI algorithm might confidently label a photo of a dog wearing sunglasses as a completely different animal or fail to recognize a stop sign if it's partially covered by graffiti. As these models become larger and more complex, these kinds of errors become more frequent, revealing a growing gap between how AI and humans perceive the world.

Recognizing this challenge, researchers funded in part by the U.S. National Science Foundation propose to combine insights from psychology and neuroscience with machine learning to create the next generation of human-aligned AI. Their goal is to understand how people process visual information and translate those patterns into algorithms that guide AI systems to act in similar ways.

The Click Me game plays a central role in this vision. In the game, participants click on parts of an image they believe will be most informative for the AI to recognize. The AI only sees the parts of the image that have been clicked. Therefore, players are encouraged to think strategically about the most informative parts of the image rather than clicking at random to maximize the AI's learning.

The AI-human alignment occurs at a later stage, during which the AI is trained to categorize images. In this "neural harmonization" procedure, the researchers force the AI to focus on the same image features that humans had identified – those clicked during the game – to make sure its visual recognition strategy aligns with that of humans.

What makes this project especially remarkable is how successfully it has engaged the public. NSF funding has allowed the team to attract thousands of people to participate in Click Me, helping it gain attention across platforms like Reddit and Instagram, and generating tens of millions of interactions with the website to help train the AI model. This type of large-scale public participation allows the research team to rapidly collect data on how people perceive and evaluate visual information.

At the same time, the team has also developed a new computational framework to train AI models using this kind of behavioral data. By aligning AI response times and choices with those of humans, the researchers can build systems that not only match what humans decide, but also how long they take to decide. This leads to a more natural and interpretable decision-making process.

The practical applications of this work are wide-ranging. In medicine, for instance, doctors need to understand and trust the AI tools that assist with diagnoses. If AI systems can explain their conclusions in ways that match human reasoning, they become more reliable and easier to integrate into care. Similarly, in self-driving cars, AI that better understands how humans make visual decisions can help predict driver behavior and prevent accidents. Beyond these examples, human-aligned AI could improve accessibility tools, educational software and decision support across many industries. Importantly, this work also sheds light on how the human brain works. By emulating human vision in AI systems, the researchers have been able to develop more accurate models of human visual perception than were previously available.

This initiative underscores why federal support for foundational research matters. Through NSF's investment, researchers are advancing the science of AI and its relevance to society. The research not only pushes the boundaries of knowledge but also delivers practical tools that can improve the safety and reliability of the technologies we use daily. ❖

Appointments

South County Health appoints four providers to oncology service line

WAKEFIELD — As South County Health recently announced the appointment of four providers across its oncology service line, strengthening capabilities in medical, radiation, and surgical oncology.


Nancy McKinney, MD

Medical Oncology

NANCY MCKINNEY, MD, a board-certified hematologist and medical oncologist who has been caring for patients in the Cancer Center as a locum provider since October 2024, has officially accepted a permanent position with South County Health.

Dr. McKinney has over 20 years of oncology experience, including clinical roles at Dana-Farber/Brigham and Women's Cancer Center, and the Hudner Oncology Center at Saint Anne's Hospital.


Michelle Viveiros, DNP

With a renewed focus on continuity and expanded access, South County Health also welcomed **MICHELLE VIVEIROS, DNP**, an advanced practice provider with over 25 years of healthcare experience, wiith a strong background in oncology nursing and a patient-centered approach.

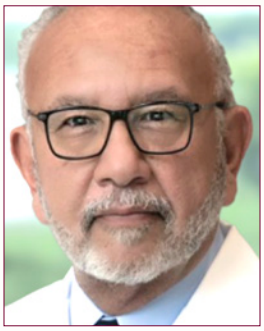

James Assif, MD

Radiation Oncology

JAMES ASSIF, MD, a radiation oncologist, will join the oncology team in August. Dr. Assif will work at South County Health Radiation Therapy, further expanding access to expert radiation services in our community.

Surgical Oncology

Additionally, long-time medical staff member **N. JOSEPH ESPAT, MD**, has accepted a position as surgical oncologist at South County Health. Trained at the Memorial Sloan-Kettering Cancer Center, Dr. Espat has more than 35 years of surgical experience and held various leadership roles, including most recently serving as the Chair of Surgery Department and Chief of Surgical Oncology at Roger Williams Cancer Center. He will officially join the team in August. ❖


N. Joseph Espat, MD

AMA announces leadership roles for 2025–2026

CHICAGO — The American Medical Association (AMA) introduced the 21 members of its Board of Trustees for the coming year following elections held during the annual meeting of the AMA House of Delegates. They are:

BOBBY MUKKAMALA, MD, an otolaryngologist from Michigan, was sworn in as AMA president for a one-year term He succeeds **BRUCE A. SCOTT, MD**, an otolaryngologist from Kentucky. With the conclusion of his presidential term, Dr. Scott is the AMA immediate past president.

WILLIE UNDERWOOD III, MD, MSc, MPH, a urologic surgeon from New York, was voted president-elect of the AMA. Dr. Underwood will become AMA president in June 2026.

DAVID H. AIZUSS, MD an ophthalmologist from California is the new chair of the AMA Board of Trustees.

TOLUWALASÉ A. AJAYI, MD, a pediatrician, adult and pediatric palliative medicine physician, and clinical translational researcher from California, is the new chair-elect of the AMA Board of Trustees. ❖

Recognition

Yashaswini Singh, PhD, named 2025 Aspen Ideas Health Fellow

PROVIDENCE – **YASHASWINI SINGH, PhD**, assistant professor of health services, policy and practice at the Brown University School of Public Health, has been named a 2025 Aspen Ideas Health Fellow by the Aspen Institute.

Its 2025 Fellows, a group of 100+ leaders from some 71 cities in 26 states in the US and four other countries around the globe. Nominated by senior Aspen Institute staff, Aspen Ideas: Health advisors, previous Fellows, and many others, these trailblazers were selected for their significant accomplishments and proven ability to transform ideas into action.

"I am excited to bring my ideas about the corporate transformation of medicine to the Aspen Ideas fellowship," Dr. Singh said. "This year's conference theme, Payoff: Investing in Health, closely aligns with my research interests and expertise that examines how market forces, such as health care consolidation and private equity investments, shape health care delivery and access."

[PHOTOS: BROWN UNIVERSITY SCHOOL OF PUBLIC HEALTH; ASPEN INSTITUTE]

In June she joined more than 100 Fellows from around the world for the Aspen Ideas health conference in Colorado: a renowned event dedicated to elevating thought leaders and driving progress in public health.

"I am thankful to my collaborators and students who have contributed to my work and thrilled to be a part of this important conversation alongside leaders who are reimagining what our health system can and should be," Dr. Singh said.

For more information, visit: https://www.aspenideas.org/articles/2025-aspen-ideas-health-fellows. ❖

[PHOTO COURTESY OF KENT HOSPITAL]

Total Joint Center at Kent awarded The Joint Commission's Gold Seal of Approval® for Advanced Total Hip and Knee Replacement Recertification

WARWICK — The Total Joint Center at Kent Hospital announced that it has again earned The Joint Commission's Gold Seal of Approval® for Advanced Total Hip and Knee Replacement Recertification. The recertification follows a rigorous, unannounced onsite review, during which Joint Commission experts assessed compliance with advanced disease-specific care standards, including the use of evidence-based clinical practices, coordinated multidisciplinary care, and patient education and outcomes tracking.

"The Gold Seal of Approval® is a symbol of quality that reflects an organization's commitment to providing safe and effective patient care," said **JENNIFER LA LUZ**, Executive Director of Operations at Kent Hospital. "This recertification reaffirms our dedication to delivering outstanding orthopedic outcomes and our ongoing efforts to meet the highest standards of care for our patients."

"This recognition is a testament to the hard work and dedication of our entire team," said **BRANDON LENTINE**, Medical Director of the Total Joint Center. "We are honored to receive this recertification and will continue to strive for excellence in joint replacement care."

The Joint Commission's Advanced Certification in Total Hip and Knee Replacement is awarded in collaboration with the American Academy of Orthopedic Surgeons and is considered the premier credential for joint replacement programs in the United States. ❖

Recognition

Blue Cross & Blue Shield of RI recognized as one of the 50 most community-minded companies in the US

PROVIDENCE — Points of Light, the world's largest organization dedicated to increasing volunteering, has named Blue Cross & Blue Shield of Rhode Island (BCBSRI) a 2025 honoree of The Civic 50, which through an annual survey recognizes the top community-minded companies in the United States.

For more than a decade, The Civic 50 has served as the national standard for corporate citizenship and showcases how leading companies are moving social impact and community to the core of their business. This comprehensive survey for companies with annual revenues of at least $1 billion evaluates the scale, sophistication and impact of their employee volunteering, community engagement and corporate philanthropy work.

"We're extremely proud to be among just 50 companies in the country to receive this prestigious recognition. It's especially meaningful to us because we are deeply rooted in Rhode Island and serving our communities is at the core of everything we do," said BCBSRI President and CEO **MARTHA L. WOFFORD**. "From investing in organizations that deliver school-based mental health support to assisting nonprofits building affordable housing to deploying hundreds of our associates for volunteer projects around the state, we are highly focused on fostering healthy communities."

Through its BlueAngel Community Investment program, BCBSRI actively partners with non-profit organizations across the state to support their efforts to advance the health and well-being of Rhode Islanders. Focus areas include affordable housing, food security, and mental health of children, families, and older adults.

In 2024, BCBSRI associates gave 9,293 volunteer hours' worth an estimated $292,000. All together last year, the company's philanthropy benefited 265 non-profits and an estimated 264,000 Rhode Islanders.

Last year, BCBSRI held its 13th annual Blue across Rhode Island day of service. More than 550 associates fanned out across the state in organized teams and spent the workday completing projects for organizations that applied for volunteer help. Blue across Rhode Island is one of the largest company-sponsored volunteer events of its kind in the state.

Another annual BCBSRI community initiative is the RI Life Index, a survey that gathers Rhode Islanders' perceptions about their ability to be healthy and well. In 2024, for the sixth consecutive year, the survey explored such topics as affordable housing, food security, cost of living, job opportunities, and education. The Index, a partnership with the Brown University School of Public Health, guides BCBSRI's philanthropy and its results are shared with elected officials, community advocates and nonprofit organizations, many of which serve on the Index's advisory coalition.

"Being named to The Civic 50 reflects our deep commitment to community and our desire to have a meaningful social impact," said **CAROLYN BELISLE**, vice president of corporate social responsibility at BCBSRI. "Our focus on philanthropy and volunteering strengthens not only who we are as a company but also how we serve our members and neighbors every day, We're grateful to our colleagues who generously commit their time and energy and to the community-based organizations with whom we partner to improve Rhode Islanders' quality of life."

JENNIFER SIRANGELO, president and CEO, Points of Light, said, "In an ever-evolving landscape, companies are looking to ensure that they can meet the needs of their communities, customers, and stakeholders. Companies like Blue Cross & Blue Shield of Rhode Island are leading the way in showing how social impact benefits their employees' well-being, strengthens the communities where they do business, and brings value and meaning to their work. Their efforts provide a model for others looking to bring the benefits of volunteering and social impact to their workforce and they're extremely deserving of this recognition."

The Civic 50 survey is administered by True Impact, and the results are analyzed by VeraWorks. The survey instrument consists of quantitative and multiple-choice questions that inform the scoring process. The Civic 50 is the only survey and ranking system that exclusively measures corporate community engagement. ❖

Recognition

Providence Veterans find way to serve again, this time through research

PROVIDENCE — Recently **KENNETH LEWIS** became the 5,000th Veteran from the Providence VAHCS to join the Million Veteran Program (MVP), the VA's largest research effort. MVP is working to improve Veteran lives by studying how genes, lifestyle, military experiences, and exposures affect health. More than 1,073,000 Veterans across the nation have already joined MVP.

"We are most grateful to the 5,000 veterans in VA Providence Health Care System, who have joined MVP. They are helping us make important discoveries toward improving Veteran health," said **SATISH SHARMA, MD**, the local site investigator and a professor of medicine at Brown University's Alpert Medical School.

In a statement, the Providence VA noted that, "Thanks to Veterans like Kenneth and the more than 1,073,000 Veterans nationwide, we understand certain health conditions better than ever before. Already, we have supported the largest genetic studies to date on posttraumatic stress disorder (PTSD), major depression, and heart disease. Other areas we're researching include tinnitus, cancer, diabetes, chronic kidney disease, Gulf War Illness, endometriosis, and suicide prevention." ❖

VA Providence's **Dr. Gaurav Choudhary** (left) and **Sarah Richer** (right) present Veteran **Kenneth Lewis** with a certificate of appreciation for being the 5000th Veteran from VA Providence to join the Million Veteran Program (MVP).

Drs. Kwon and Renaud named Health Policy Scholars by ACS

CHICAGO — The American College of Surgeons (ACS) has named 18 surgeons 2025 Health Policy Scholars. They attended the June Leadership Program in Health Policy and Management presented by The Heller School for Social Policy and Management at Brandeis University in Waltham, MA.

Steve Kwon, MD

Elizabeth J. Renaud, MD

Each scholarship included participation in the weeklong intensive course, followed by a year's service in a health policy-related capacity for the ACS and the surgical specialty society that is co-sponsoring the awardee.

Representing Rhode Island this year are:

STEVE SUNG KWON, MD, MPH, MBA, FACS a surgeon at the Roger Williams Medical Center in Providence and recently promoted to Associate Professor of Surgery at Boston University Chobanian & Avedisian School of Medicine (Americas Hepato-Pancreato-Biliary Association Health Policy Scholar).

ELIZABETH J. RENAUD, MD, FACS, a surgeon at Rhode Island Hospital and Hasbro Children's Hospital in Providence (New England Surgical Society Health Policy Scholar). ❖

Obituaries

ARTHUR ANDREW FRAZZANO, MD, 75, passed away on June 2, 2025. He earned his Bachelor of Science in Biology from Seton Hall University, followed by a Master of Medical Science and Doctor of Medicine from Rutgers Medical School. He then completed four years of postgraduate training at Brown University's Alpert Medical School, where he would later leave a lasting legacy as both a clinician and educator.

Dr. Frazzano spent nearly two decades practicing family medicine in Portsmouth, Rhode Island, providing comprehensive high-quality care across office visits, home visits, and nursing home services. He was a tireless advocate for public health, serving as President of both the Rhode Island Academy of Family Physicians and the Rhode Island Medical Society. He took great pride in launching Tar Wars, a statewide anti-tobacco education program for schoolchildren.

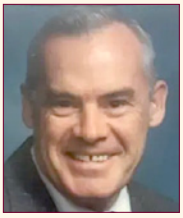
After his years in private practice, he returned to Brown University as a dedicated medical educator, training the next generation of physicians. For over 20 years, he mentored students and residents, helped establish the foundational "Doctoring" course, and served as Brown's Associate Dean of Clinical Faculty. His passion for teaching earned him numerous accolades, including the Charles Hill Award recognizing leadership and service, an honor he held especially close to his heart.

His personal life was rooted in love and devotion to his family. He is survived by his wife, Irene Frazzano; his children, Rebecca, Kristina, and Andrew Frazzano; their spouses, Evan Meagher and Leah Frazzano; and his cherished grandsons, Wes Sodl, Joseph Frazzano, Benjamin Frazzano, and Jude Meagher.

He cherished his role as a father and grandfather. He spoke often of how much his children meant to him and how much he missed them after they left home to build families and successful careers of their own. His pride in their paths was matched only by the love he carried for them: steady, unwavering, and central to his life. In his later years, Arthur faced blood cancer with tenacity and grace, participating in clinical trials to help advance treatments for multiple myeloma in an act that embodied the same devotion to service in medicine that defined his life.

The family welcomes donations in his memory to the Cancer Center at Massachusetts General (https://giving.massgeneral.org/donate/cancer-center) or to St. Jude Children's Research Hospital (www.stjude.org/donate/donate-to-st-jude.html).

He will be remembered not only for his extraordinary career, but also for the warmth, compassion, and quiet strength he brought to those around him. His legacy lives on in his patients, students, friends, and family, whose love for him is enduring and boundless. ❖



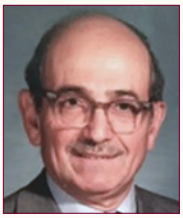
EDWARD JENCKS GAUTHIER, MD, passed away June 16, 2025 after suffering a stroke in July of 2018. A graduate of Hope High School, he continued his studies at Brown University majoring in English. He graduated with distinction as a member of Phi Beta Kappa in 1954. He then went on to Tufts University School of Medicine and graduated in 1958.

Dr. Gauthier then completed a fellowship and residency cardiology in Rhode Island in 1963. He became board-certified in internal medicine, which began a long career in that field. He continued in private practice from 1971-2005. He later began a Primary Nursing Home Practice, which he was dedicated to until 2018.

Outside of his career, he had a wide array of interests which included fishing and sailing. He was an avid reader of literature and historical studies. In addition, he had an artistic side which he expressed through his paintings.

He leaves behind his wife, Mary, sons Edward N. Gauthier, David G. Gauthier and his wife Susan, granddaughter Nicole, his sister Amy Mullervy and husband Miles, and nephews and nieces.

Donations in his memory may be made to West View Nursing Home, Activities Department, Attn: Matt Cooper, 239 Legris Ave, West Warwick, RI, 02893. ❖



DR. YOUSSEF HABIB GEORGY ("Gorgi"), 96, of Providence, passed away on May 26, 2025. Born on July 6, 1928, in Cairo, Egypt, he is survived by his sons, Habib Y. Gorgi, and his wife Susan of Providence, and Michael Y. Georgy of Dubai, as well as his six beloved grandchildren. He was predeceased by his beloved wife Bouva, whom he was married to for 65 years.

A devoted physician, he began his distinguished medical career in Egypt in the early 50s. In January of 1967, he and his wife immigrated to the United States with their two young sons. They made their home in Providence, where he had to restart his medical career as an intern at Miriam Hospital. He then joined Rhode Island Hospital where he completed his residency and fellowship in internal medicine and cardiology.

He and his family eventually moved to Cumberland, where he established his medical practice. He served generations of patients with unwavering dedication, continuing to care for others until the age of 90 – a testament to his extraordinary work ethic and deep sense of purpose.

His proudest role was that of a father and grandfather ("Geddo"). His family was his greatest joy and lifelong motivation. He

offered his love unconditionally, his support unwaveringly, and his wisdom freely. His legacy of respect, humility, warmth, humor, and resilience lives on in his children and grandchildren.

Dr. Georgy lived a life defined by his faith, compassion, dedication, and love. His was a life well lived, and his memory will be forever treasured by all who knew him.

Donations may be made in his memory to St. Sebastian Catholic Church, 67 Cole Avenue, Providence, RI, 02906. Condolences may be left at monahandrabblesherman.com. ❖

VINCENT F. GEREMIA, Jr., MD, 88, of Bristol, RI died unexpectedly Sunday, June 22nd. He was the loving husband of Brenda A. Geremia.

He graduated from Cranston High School in 1955, Brown University in 1959, and Yale Medical School in 1963. Dr. Geremia was a Vietnam veteran, rising to the rank of Lieutenant Commander in the U.S. Navy and was stationed at the Newport Naval Hospital after his tour in Vietnam. He was a well-known and highly respected anesthesiologist for over 30 years, working at Truesdale Hospital and later as the Chief of Anesthesia at Charlton Memorial Hospital in Fall River, MA.

Dr. Geremia was a 54-year resident of Bristol, RI, a member of Bristol Rotary, and a long-time volunteer at Rogers Free Library where he built many of the props for the children's program.

In addition to being a devoted husband, father, and grandfather, he was a kindhearted man to all who knew him including his family, friends, and neighbors.

In addition to his wife, he is survived by his two sons, Timothy Geremia (Mary Lynn) of Wakefield, and Matthew Geremia (Christine) of Lake Worth, FL, and his three granddaughters Allison Geremia of Savannah, GA, Kasey Feijo (Jordan) of Bristol, RI, and Alexandra Geremia of Wakefield, RI. He is also survived by his sister, Norma Paliotti of Cranston, RI, and his brother, Robert Geremia (Eileen) of Altoona, FL.

Memorial donations may be made to the American Heart Association or Friends of Rogers Free Library. ❖

JOHN W. HAYES, MD, 82, of East Greenwich, passed peacefully on May 30, 2025, surrounded by his family. Born at home in Cranston, he was the son of the late Walter E. Hayes, MD, and Evelyn Hayes. He was married to his beloved wife, Charlotte, for 60 years. They began their journey together as teenagers, married as recent college graduates and returned to Rhode Island to build their legacy amongst family.

He often recounted the joys of his childhood at Bonnet Shores beach and preached the academic rigor of his favorite school, Classical High School. After Classical, he earned his undergraduate degree, cum laude, from Boston College and his medical degree from McGill University School of Medicine, where he achieved the distinction of the Alpha Omega Alpha Honor Medical Society. He was particularly proud of his service in the United States Navy, where he attained the rank of Lieutenant Commander while stationed at the Patuxent River Naval Air Station.

Following his honorable discharge from the United States Navy, he returned home and began his career in orthopedics under the tutelage of the late A.A. Savastano, MD. At the urging of his longtime friend and colleague, the late Paul Poirier, MD, he started his own practice in orthopedic surgery in Warwick, at Kent Hospital, where he earned the designation of Diplomate from the American Board of Orthopedic Surgery, and later served as the Chief of Orthopedics. During his time at Kent, Dr. Hayes served in various capacities at the Rhode Island Medical Society, the Kent County Medical Society, the Rhode Island Orthopedic Society, Kent Hospital's Board of Directors and Kent's parent entity, Care New England.

He took great pride in overcoming the perils of alcohol addiction and, over the last half of his life, Jack found purpose in his service to the Physicians Health Committee, where he helped scores of physicians and medical professionals overcome their own struggles with alcohol and addiction.

A long-time member of Warwick Country Club, Point Judith Country Club, and the Dunes Club, his perfect day began with a very early morning round of golf with his sons, followed by an afternoon parked in a beach chair on the sand alongside his wife, daughter, and a challenging crossword puzzle, before closing the day by manning the grille outside his favorite house in Narragansett – a full "Dr. Jack" day, indeed.

In addition to his wife, Dr. Hayes is survived by his children, Jack, Jr. and his wife, Bridget; his daughter, Suzanne and her husband, Chet Trossman, and his son, Steven and his wife, Julie, and his much-loved grandchildren. He also leaves behind a brother, Brian E. Hayes, of Virginia, and a sister-in-law, Anne Greason, of Narragansett.

To share memories and condolences, please visit: www.TheQuinnFuneralHome.com. ❖