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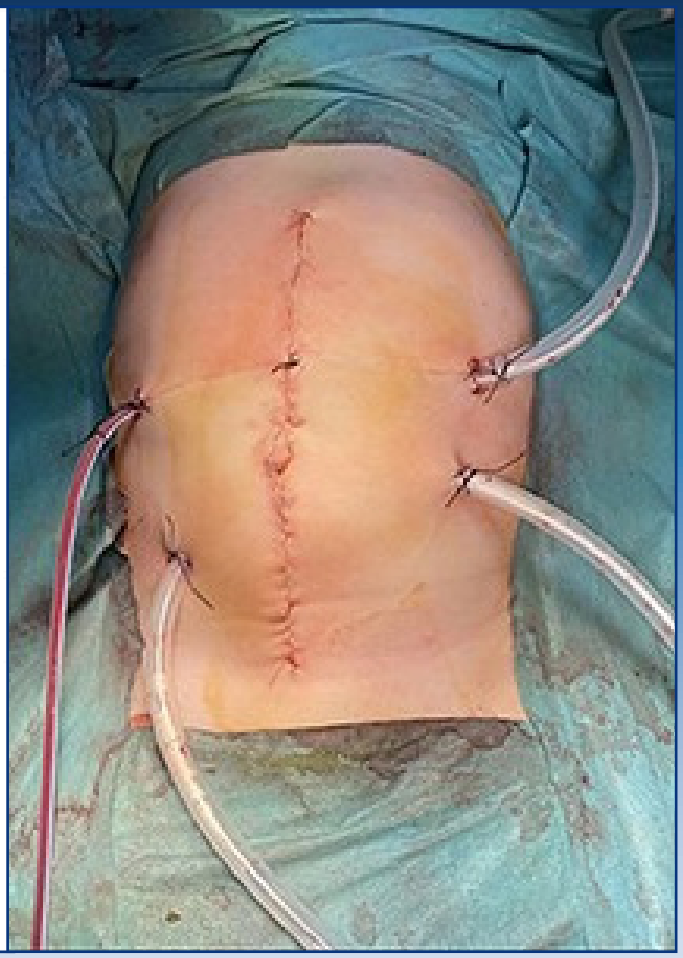

SPECIAL SECTION

UPDATES *in* SURGICAL ONCOLOGY

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

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Steve Kwon, MD, MPH

SPECIAL SECTION

Updates in Surgical Oncology

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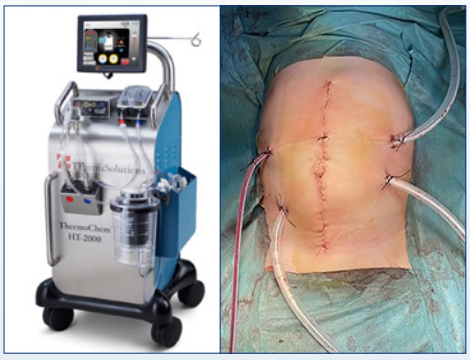

Cover images are from theme article "Current Applications of Intraperitoneal Chemotherapy" and show HIPEC machine (from ThermaSolutions) and intraoperative set-up of HIPEC instillation – closed abdomen technique.

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.

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Guest Editor

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Regional Hepatic Therapies for Colorectal Hepatic Metastases

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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.

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Current Applications of Intraperitoneal Chemotherapy

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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

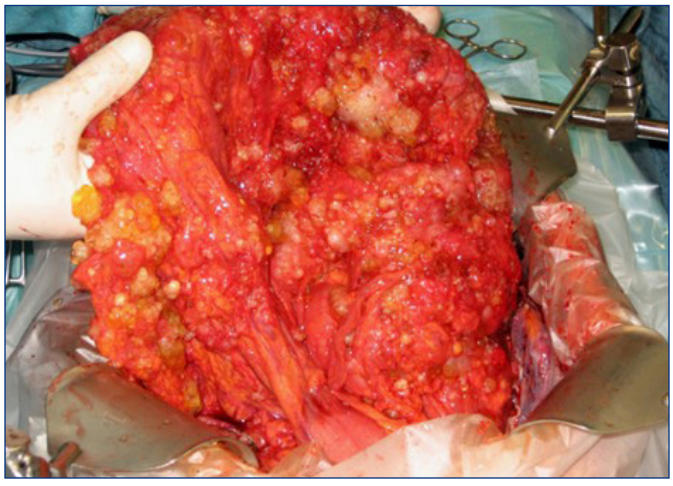
Peritoneal metastases pose a unique issue when considering treatment modalities. These tumors, often arising from colon, appendix, stomach and ovary, can be widespread, variable in size, and occupy organs with relatively sparse blood supply compared to other tumor locations.[1] Because of these characteristics, 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]

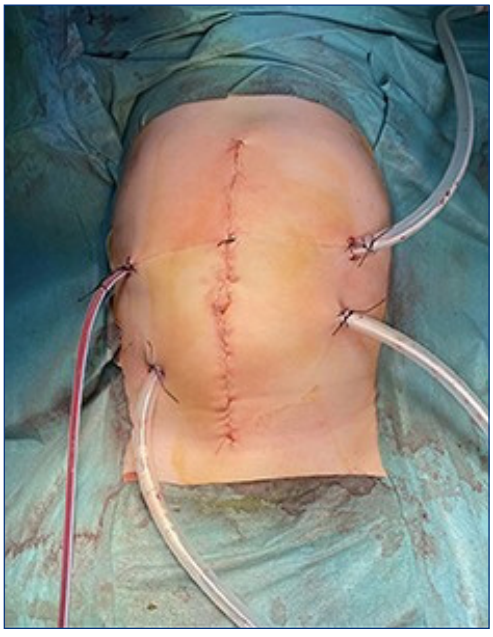
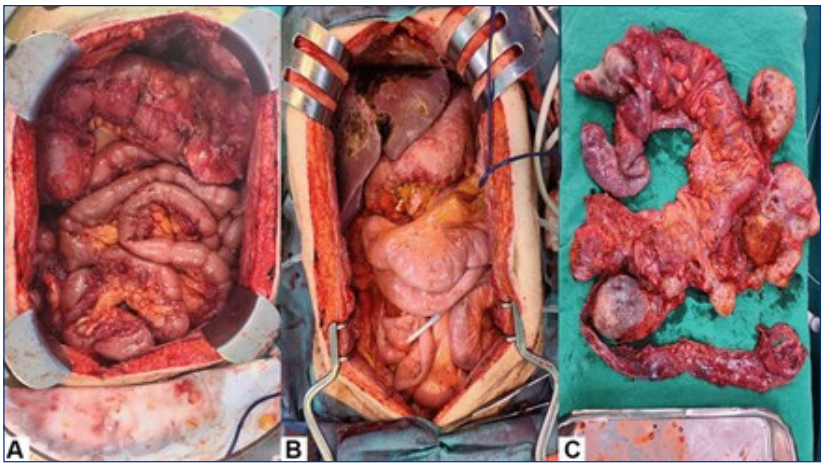


Figure 4. Before and after cytoreductive surgery with HIPEC30. [**A**] Before cytoreduction; [**B**] After cytoreductive surgery; [**C**] Tumor with involved organs removed



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.

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Disclosures

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Minimally Invasive Liver Surgery for Primary and Secondary Liver Malignancies

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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.

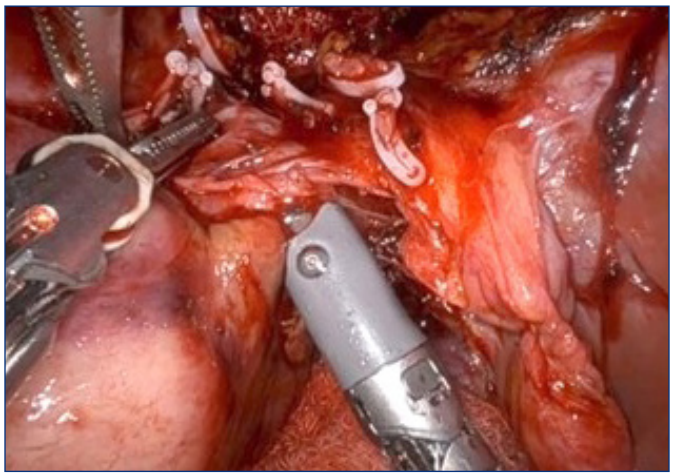
GLISSONIAN PEDICLED APPROACHES

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]

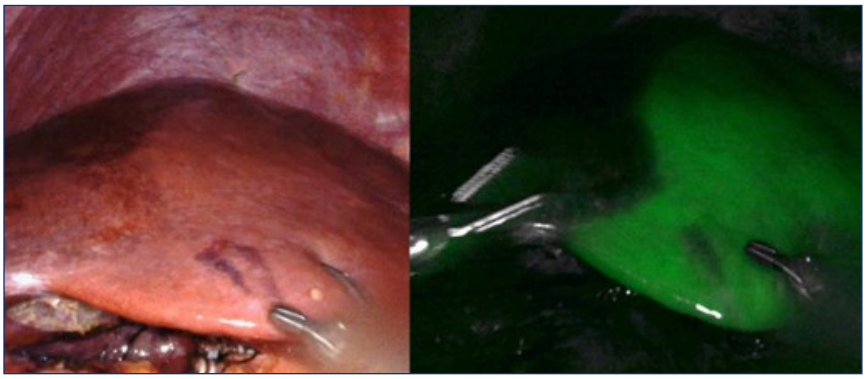
MINIMALLY INVASIVE MAJOR HEPATECTOMY

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)

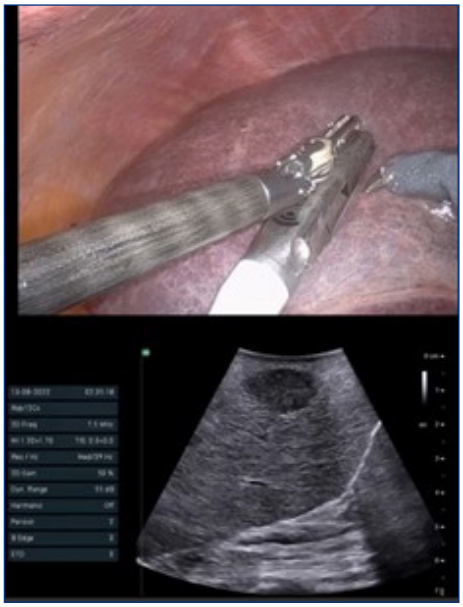
Due to the intricate anatomy and 3D contouring of the liver segments, non-anatomic parenchymal sparing resections can be technically challenging. Use of adjuncts such as intra-operative ultrasound (IOUS) and ICG fluorescence can help with adequate mapping of tumors in relation to vasculo-biliary pedicles. 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.

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Emerging Technologies for Pancreas Resection

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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.

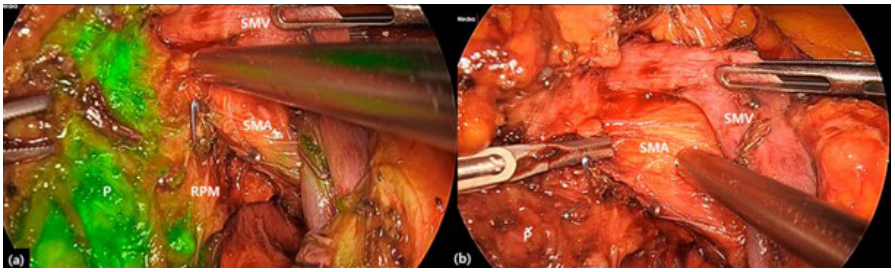
MINIMALLY INVASIVE TECHNIQUES

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]

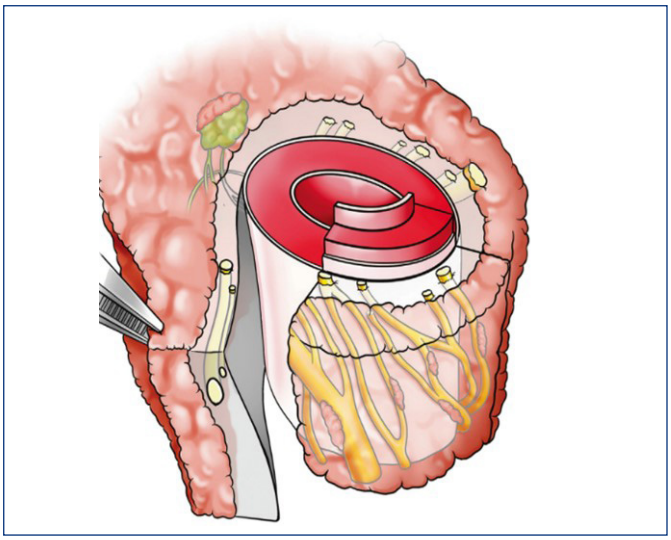
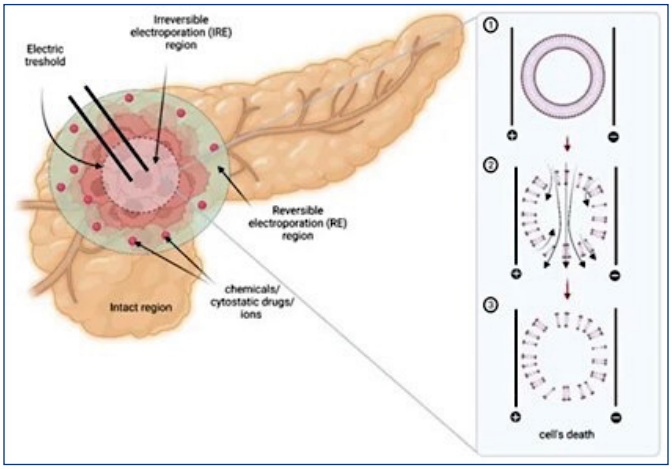


Figure 3: Irreversible electroporation electrodes surrounding pancreatic tumor.[23]



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.

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

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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.

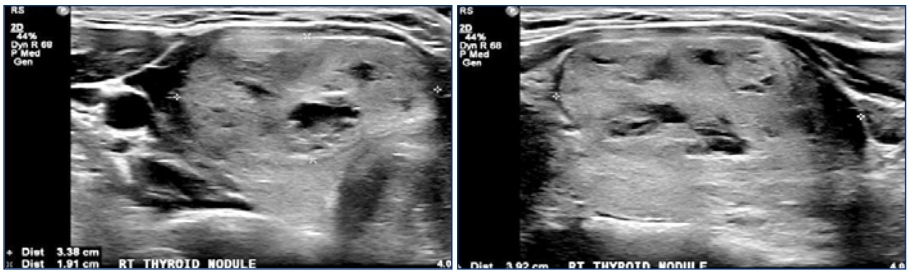
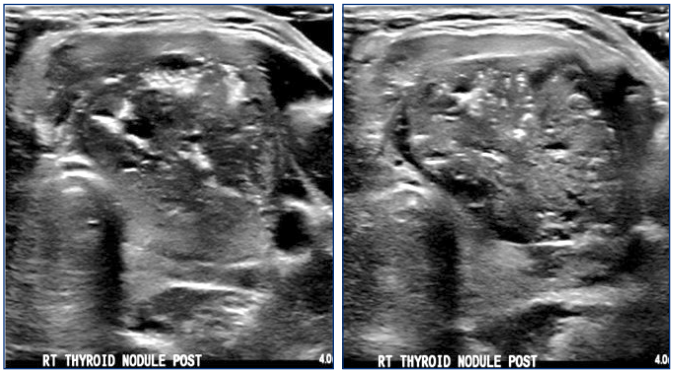


Figure 1C,D. Post-procedure imaging demonstrating post radiofrequency ablation changes including areas of hyperechogenicity without evidence of immediate complications.



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.

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

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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

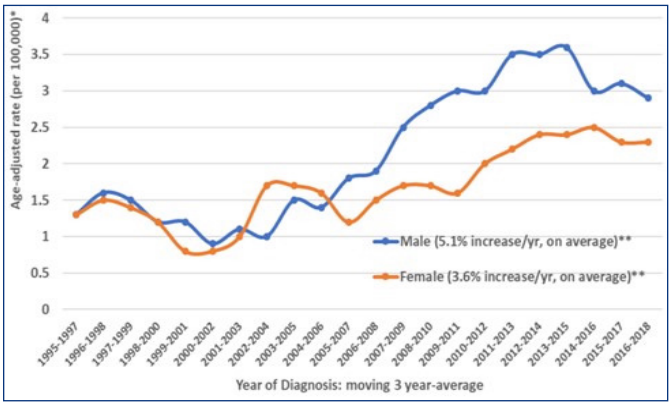


Figure 2. Age at diagnosis of Cholangiocarcinoma by sex from 1995 to 2018

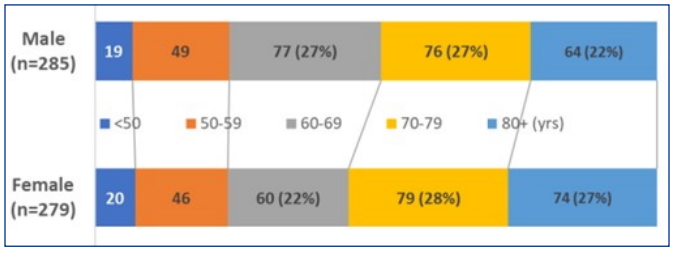


Figure 3. Incidence (rate) by sex and race/ethnicity from 1995 to 2018

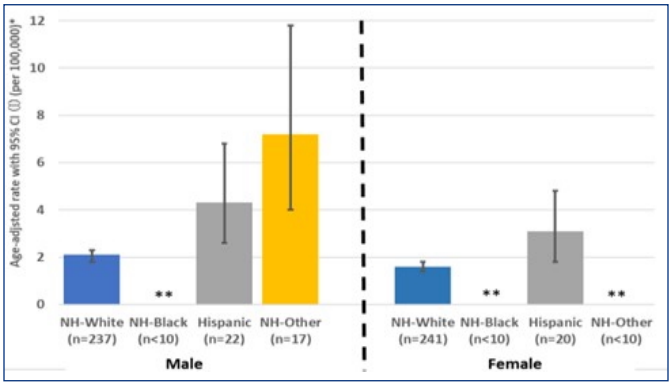
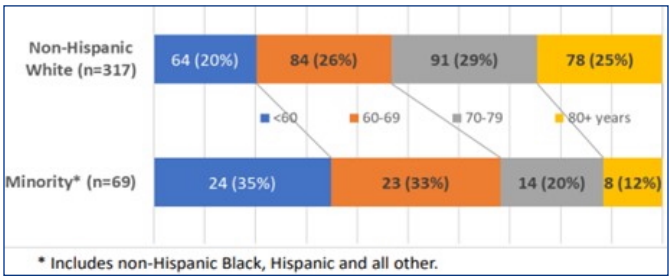


Figure 4. Age at cholangiocarcinoma diagnosis by race/ethnicity from 2007 to 2018



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.

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Disclosures

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