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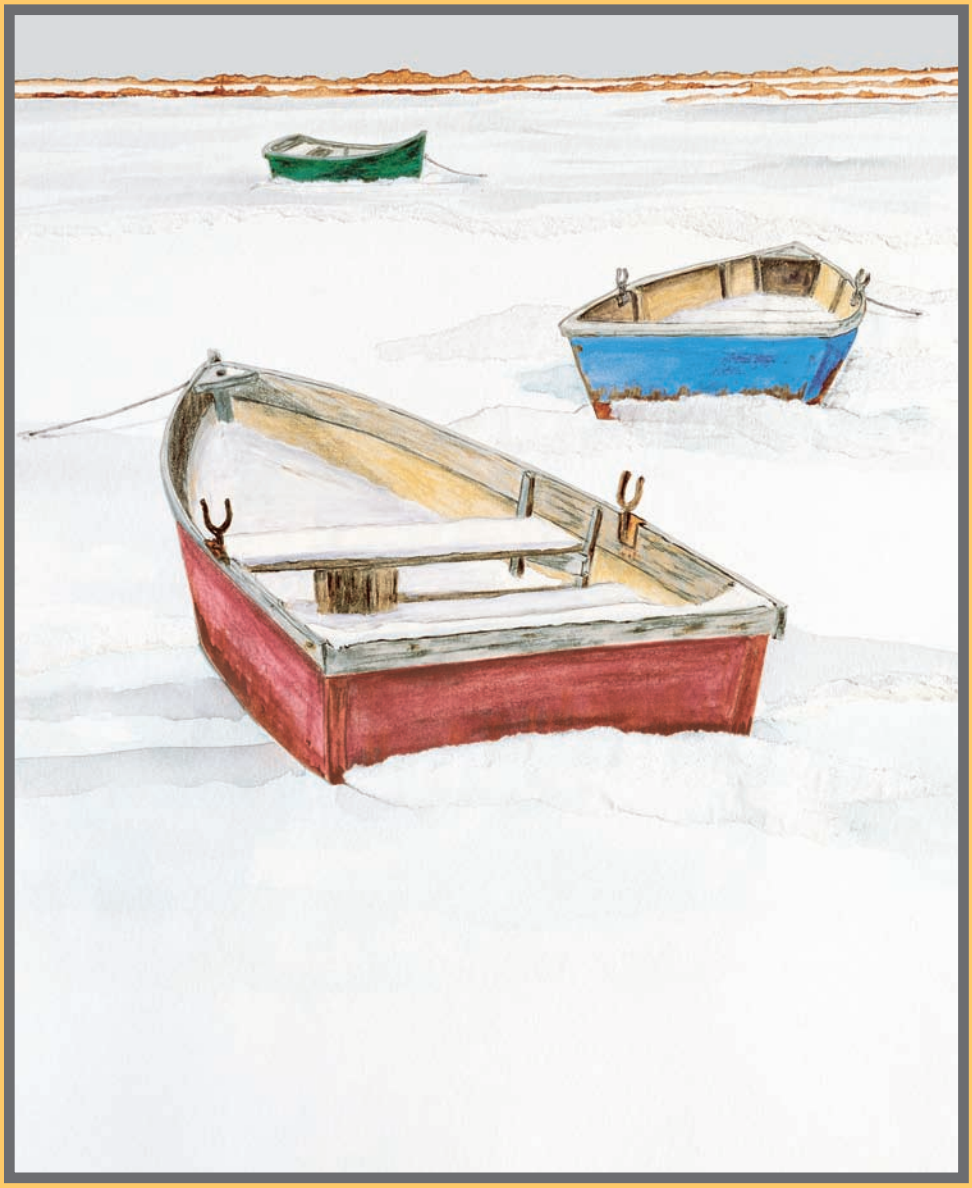

SPECIAL ISSUE: RADIATION ONCOLOGY

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Commentaries

Culture gaps

I am not a sensitive person. Of course, like everyone else I'd like to think I am. But that's the feedback I often get from some people. And, being insensitive, there's a lot of feedback that I simply don't perceive. I don't mean to imply that I'm more callous than others. I don't think that's the case, just average probably, but who knows?

I recently met socially, not in my office, a deaf person, the significant other of a relative. He communicated with signs via an interpreter. I learned a little bit about the deaf community, but a lot about my own ignorance of the deaf culture. I asked a lot of questions, which were apparently considered insensitive by some observers, but not to the point of being too embarrassing or insulting. In retrospect I don't think I was either insensitive or insulting and would ask the same questions again. What I really learned that day was the fact that there is a deaf culture that is a distinct subculture in our country, and probably in most developed (and undeveloped?) countries. I knew that books have been written about this, but I never fully appreciated the chasm between being deaf and being able to hear. I did not know that American Sign Language (ASL) had not been considered a "real" language until the 1960s, and that many, if not most, deaf children grew up without any language at all if their parents weren't also deaf. Now, as a neurologist, insensitive or not, I can fully grasp the awful impact of growing up without language through the first few years. There is a critical period after which language will never be normal, and another period after which language will never develop. Yet many deaf children were not taught ASL from the beginning, and were forced to learn lip reading, whose content is only 20-30% interpretable in the best of circumstances, and is, of course, a highly unnatural medium.

My "insensitivity" centered around my questions on growing up, learning language, learning a bit about lifestyle. I have a small background but greater interest in foreign cultures. I've spent time in three different places in Africa and am drawn to these "exotic" places largely because of the cultural differences that are so interesting. My approach to the deaf friend was, I think, no different than my approach would have been to someone from an African culture I was unfamiliar with. In Africa, where there are so many different tribes, each with its own customs and languages, people commonly ask each other about their customs. "How do you do this? What do you do if this happens?" "What's your word for this?"

Growing up as Jewish in a Christian country I was schooled very early on the ways in which my culture was different, yet it was puzzling to me that most people where I lived were Jewish. I always thought that mine was the dominant culture. When I had contacts outside my neighborhood, we almost always discussed differences between our families and their activities. My experience with the deaf man was then not unusual for me in that context.

What is striking, however, is the ease with which we doctors can take to being so cavalierly invasive of others' mores. In the office we frequently ask, and need to ask, questions that would be rude in social settings. Clearly we would never dream of asking someone at a social event if they were constipated, or had difficulty passing urine. We wouldn't ask about their mood or diet. But cultural questions are often of interest. We like to learn about things foreign to us. We may take pleasure in learning about a job that we've never encountered, a location that is foreign, a set of aspirations alien to ourselves. But being a physician may make us a little less sensitive to being invasive. We are card-carrying invasiveness technicians. This may not be a good thing. The problem is, I think, that we may have internalized aspects of our "business" personality that do not translate well into normal social interactions. The problem is, who's to tell? Am I insensitive, because I'm insensitive? Am I overly invasive because my physician's training has altered my baseline of what's considered appropriate? Or am I merely a person who enjoys learning about other cultures?

Dr. Ed Feller and his students recently contributed an article to *Medicine & Health/Rhode Island* (August 2005) on deaf patients. It is a worrisome collection of data because this group is so overlooked that they're not on most radar screens. The law requires treating doctors to hire sign language translators, at the doctor's expense, which is obviously a ridiculous notion, and probably rarely done. Perhaps a more appropriate solution would require the patient to bring either a human translator or a computerized speech interpreter. Unfortunately, not all deaf signers can read English at the required level so that a computerized speech recognition device would not suffice. I don't have a solution for this, but I do think it extremely important for us doctors to recognize the differences in our cultures, that middle class deaf people are not just like us except for the hearing. And probably the best way to learn about this is to ask the sorts of questions I asked my guest. In the doctor's office I'd make sure I learned whether the deaf patient was sufficiently literate to communicate by writing. I might not do that at home. Many are not. We doctors would certainly inquire into culture differences with patients newly arrived from other cultures, especially if we thought their approach to modern medicine may be different than ours. Being inquisitive may actually be a sincere form of sensitivity.

Joseph H. Friedman, MD

The perils and virtues of medical privacy

An ancient Saxon law forbade the construction of a residence closer than two feet from someone else's property line, thus avoiding possible injury from water running off the eaves of the newly erected building. Roman civil law, incidentally, had similar provisions protecting against harm caused by *stillicidium* [roof dripping]. These laws also guarded the privacy of the home by forbidding strangers, eavesdroppers, from standing beneath the eavesdrop. The integrity and privacy of the home, a man's castle, was thus reasonably ensured by common law.

Privacy may be broadly defined as the willful pursuit of activities, intimate or otherwise within a non-public space with neither hindrance nor fear of trespass or punishment. A complex society must limit those activities called private. One may be subject to legal restraint if one's private activities included bomb-making or holding another person against his will. But may privacy include the right to harm oneself, to plan an act of violence or to engage in unconventional sexual acts with another consenting adult?

Privacy, as an unalienable right, seems to be a recent historic contrivance. Certainly the constitution makes no explicit mention of it. Even the word, private, has an ambiguous etymologic history.

The Latin word, *privatus*, is defined as something belonging to an individual, but also someone withdrawn from public life, or someone apart from the State. Its past participle, *privus,* conveys the further meaning of being robbed or deprived of something. The negative quality inherent in "something apart from the State" persists in English words such as privation, private and deprive, all of which hint at something having been taken away rather than being added, that being "private" is at best a mixed blessing and at other times, a state of having been divested of something. Certainly, in terms of authority or privilege, most army recruits would not voluntarily choose the rank of private.

A desire for privacy in ancient nomadic tribes must have been considered either an idiosyncracy or more likely a madness. The tribe depended upon the exercise of uncontested authority for its survival. Its leadership – whether vested in one person or in a council of elders – could tolerate neither dissension nor pockets of privacy. Its members were first elements of the tribe, identified as part of a structured congregation called the tribe, and only belatedly as individuals each with a distinguishable agenda.

To exclude a member of the clan or tribe, as punishment, was a penalty virtually equivalent to death since each member's center of gravity and very identity lay within the tribe rather than within himself. And to be so punished, whether it be called ostracism or excommunication, was therefore a terrible forfeiture of human identity.

But society has matured since the days when the source of the evening meal and finding a place of secure shelter were the dominant objectives of the group; and members of the tribe are no longer referred to as its children. Progress in achieving an abundance of food and other staples, in many developed nations, now allows adults to choose their own vocations, to think independently and to dissent when warranted. Western civilization prospers most when it represents a gathering of tolerant people with diverse opinions, faiths and priorities and with a government which values privacy and individual creativity.

The corporate nature of modern medicine, with its battalions of clerks, insurance companies and administrators, makes medical privacy an unrealizable goal. Physicians take the Hippocratic oath: "And whatsoever I shall see or hear in the course of my profession…I shall never divulge, holding such things to be holy secrets." Yet patients' names and intimate details were readily disclosed even in Hypocrites' published case histories.

Medical confidentiality, integral to that precious tapestry called civil liberties, is a comforting concept. But medical privacy is repeatedly, routinely, violated by two forces: the need of insurers, public or private, to know what they are paying for; and the need of the public to identify, and have treated, those individuals whose private diseases constitute a measurable public health hazard.

If human illness were merely a personal matter never affecting the health of others, there would be little demand for health regulations of the deliberate invasion of private medical records. These records, as with each person's bank account or sex life, would then remain a strictly personal matter.

But an unresolved tension persists, with no simple solution, between the right of privacy and the need to preserve the health of the community. Consider, for example, the following situation:

The year is 1906 and New York City physicians trace clusters of typhoid fever cases to an itinerant cook named M.M., who was shown to be a carrier of the germs of typhoid fever. Despite appeals that she cease working as a cook she persisted; and in less than a year she had infected a verified 55 cases [epidemiologists claim that the number was well over one thousand.] M.M. was finally arrested and isolated for 35 months [during which time, no new cases of typhoid arose.] In 1910 she was offered freedom on the condition that she avoid employment as a cook. She was released, promptly changed her name and disappeared into the urban streets of New York. Another outbreak of typhoid in 1915 was traced to her, and she was again placed in a quarantined cottage and confined there until a stroke killed her in 1938.

Did society have the right to protect itself by indefinitely imprisoning a woman who was blameless – except for her egregiously unsanitary personal hygiene?

Stanley M. Aronson, MD

Introduction: Radiation Oncology for the 21st Century – The Best Is Yet To Be

Arvin S. Glicksman, MD

The use of radiation has been a major contribution to oncology in the 20th century. Shortly after the separation of radium by the Curies and Beckerel, its potential biological effects were recognized by Pierre Curie. Henri Beckerel had placed a planchette of radium salt in his vest pocket. Three or four days later he noted a red patch on his skin. Pierre immediately appreciated the biological activity and sent a small supply of radium to the Hotel D'Dieu, where it was used experimentally for various surface cancers. By 1901, Mary Cleeves published the first paper on the use of radium planchettes placed in contact with cervical cancer; by 1907 papers appeared on the use of both external beam radiation and surface radium packs for breast cancer. Alexander Graham Bell wrote to the Curies, suggesting that radium salts could be placed in hollow tubes and inserted directly into solid tumors, thereby irradiating the tumors from the inside not just from the surface. From this, the entire program in brachytherapy has evolved.

Both the public and the medical profession showed "an irrational exuberance," applying radium salts, radium water, and radium packs for all kinds of benign as well as malignant conditions. Slowly, but inevitably, the use of radiation for benign conditions was found to have its downside. Madame Curie's aplastic anemia, the bone cancers of the radium dial painters in World War I, the radiation-induced skin cancers, and deep seated cancers associated with the treatment of acne and or arthritis had a sobering effect; but the late effects of the Hiroshima/Nagasaki experience gave us a whole library on the biological effects of ionizing radiation.

On the other hand, the research that led to the atomic bomb produced, as a byproduct, radioactive cobalt and other radioactive isotopes, which have found their way into clinical medicine. The World War II research on radar led to the development of the Clystron, which became the major component of linear accelerators. The development of computers in the 1960s led to the application of computer technology in radiation oncology. This was actually pioneered at the Radiation Oncology Department at the Rhode Island Hospital in the 1970s to 1980s. The continued refinement and power of computer technology and its application to radiotherapy has advanced beyond our wildest dreams when we set up the first program in 1973.

Although radiation oncology depends upon the technical capabilities of computers, linear accelerators, and improved imaging, the application of these technologies oncological conditions is the basis of the discipline. Thus the Radiation Oncologist is a member of an oncology treatment team. Radiation Oncology contributes to cancer management by integrating radiation pre-op, post-op, or with neoadjuvant and/or adjuvant chemotherapy. Basically this integration is best done not as an individual discipline but as a member of a treatment team with planned management developed by the entire team to the patient's benefit.

Radiation oncologists have always wished to be able to treat the malignancy effectively, sparing the normal tissue of deleterious radiation effects. Megavoltage (over 1 million) of the 1970s was a step better than supervoltage of the 1960s and this was a leap forward better than orthovoltage (250 KV) of the 1940s. With each improvement deep-seated tumors came within the beam's useful range, more effectively sparing the normal overlying tissue from excess radiation. By beam shaping and more recently with **Intensity Modulated Radiotherapy (IMRT**) and **Image Guided Radio-Therapy (IGRT)** significant normal tissue sparing has become part of standard radiotherapy, allowing for increasing cancerocidal doses of radiation to be delivered without unacceptable normal tissue doses. These refinements in beam placement on tumor-bearing tissue with little or no dose to surrounding normal tissue requires a well defined three dimensional visualization of the tumor in relation to the anatomical region. This could not be accomplished without the advanced diagnostic images from CT scans, MRI, ultrasound and PET scans.

The use of radioactive isotopes in plaques, seeds or ribbons has always been an attractive way of delivering cancerocidal radiation limiting the normal tissue doses. It has been a standard of treatment for gynecological malignances; in head and neck cancer; many deep seated tumors in conjunction with surgery; and in the last decade has become a regular treatment of prostate cancer.

The opportunity to target individual cancer cells with radioactive tagged monoclonal antibodies has emerged as an exciting modality and has proven useful for malignant lymphomas, adding to our abilities to control a group of malignancy. The full potential for this approach will emerge in the 21st century.

We stand at a junction where improved technology provides ever-increasing sophisticated radiation management of cancer. There remains great excitement and enthusiasm among radiation oncologists.

The best is yet to be.

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Combination Chemotherapy and Radiation Therapy for Upper Aerodigestive Tract Cancers

Timothy D. Shafman M.D.

For the purpose of this article, "upper aerodigestive tract tumors" will include head and neck cancers and esophageal cancers. The treatment of patients with these different tumors demands a multidisciplinary approach. A radiation oncologist, a medical oncologist and a specialty surgeon comprise the backbone of the team, which also includes radiologists, pathologists, dentists, specialized nurses, pain management specialists, rehabilitation specialists (e.g., speech and swallowing therapists), nutritionist, social workers and supportive family members. While the input of all these caregivers is paramount in the successful treatment of these diseases, this review will focus on the use of chemoradiation.

Head and Neck Cancers

Head and neck cancers include tumors of the lip, oral cavity, oropharynx, hypopharynx, supraglottic larynx and glottic larynx, paranasal sinuses, nasopharynx and major and minor salivary glands. Approximately 40,000 cases of head and neck cancer will be diagnosed this year while an estimated 11,000 deaths will be caused by these tumors.[1] The most common factors associated with cancers of the oral cavity, oropharynx, hypopharynx and larynx are alcohol and tobacco use. With a major reduction in the use of these substances, the incidence and morbidity and mortality from head and neck cancer would be significantly lowered. Consequently, the physician should urge the patient to reduce consumption of alcohol, and to cease smoking. Furthermore, the entire upper aerodigetive tract can be exposed to these carcinogens, which can lead to the development of lung and esophageal cancers.

The TNM system of the American Joint Commission on Cancer is used for staging head and neck cancers. The staging system consists of two definitions for the primary **tumor (T stage)** based on size for lip, oral cavity and oropharynx or based on subsite and invasion of adjacent subsites for glottic and supraglottic larynx, hypopharynx and nasopharynx. Lymph **node staging (N)** is based on size, number and location and is uniform for each site except nasopharynx.

Treatment of head and neck cancer depends on the site and extent of disease at presentation. While surgery alone may be recommended for a portion of patients with early stage disease, radiation therapy alone and/or chemoradiation may be appropriate for these patients as well as for those with locally advanced disease. The use of all three modalities has been the topic of rigorous investigations; some broad conclusions have been reached.

Radiation Therapy for Head and Neck Cancers

Radiation therapy alone has been used for decades in the treatment of head and neck cancers. Standard radiation, delivered once a day, is the most common method to deliver treatment for patients with early stage disease. This results in local control, ranging from 75% in most T2 tumors to greater than 95% for T1 larynx cancer. The most effective method of delivering the radiation in patients with more advanced local-regional disease has been controversial and studies have tested different fractionation schemes.

Accelerated fractionation was developed to overcome the potential for rapid tumor proliferation, known to occur in squamous cell carcinoma, and may result in less effectiveness when a standard once-a-day treatment schedule is used. Accelerated fractionation seeks to decrease the overall treatment time and can be accomplished by giving three fractions-a-day as in some Europeans protocols or by delivering a boost of radiation as a second daily fraction for the last two weeks of treatment as in recent USA trials. The total treatment time decreases from 7 weeks to 5-6 weeks.

Hyperfractionation takes advantage of the capacity of normal tissue to repair from radiation-induced DNA damage. The goal is to increase the overall total dose while sparing normal tissue by delivering smaller fractions of radiation. The typical method is to deliver 1.2 Gy fractions twice a day to a total dose of 81 Gy, compared to the standard 2.0 Gy once a day to a total dose of 70 Gy, both delivered over 7 weeks.

Three large Phase III trials have compared standard fractionation to altered fractionation. All have shown a benefit to altered fractionation, compared with standard fractionation for local and regional control of tumors.[2,3,4] In Europe two separate trials comparing either accelerated fractionation or hyperfractionation with standard radiation therapy revealed a significant increase in local control of 14 to 18%; and a recent analysis has also shown a small survival benefit to hyperfractionation.[2,3] In the United States, the **Radiation Therapy Oncology Group (RTOG)** performed one trial involving 1113 patients comparing once-a-day radiation to three different altered fractionation schemes. The results revealed a significant improvement in local control, from 46% in the standard arm to 54.5% in both the accelerated and hyperfractionated radiation arms. At the first report, the study noted no survival differences.[4] Despite these improvements in local control, disease-free survival remains relatively low with altered fractionation, in the 30-40% range in these studies. Different techniques need to be developed. Concurrent chemoradiation is one such method and will be discussed further, as will newer methods to deliver radiation (intensity modulated radiation therapy) and other ways to increase the therapeutic ratio of radiation therapy.

Combined Radiation and Chemotherapy

Combined chemotherapy and radiation therapy has been studied in numerous randomized trials. One meta-analysis revealed that chemo-

therapy given before definitive surgery or radiotherapy (neo-adjuvant) did not improve local control or survival in patients with advanced stage head and neck cancer.[5] More recently, an RTOG trial revealed that the neo-adjuvant approach to larynx cancer, with larynx preservation survival as an endpoint, showed no benefit for this method compared to concurrent chemotherapy and radiation or radiation therapy alone.[6] While this approach makes sense in certain clinical situations, and is used regularly, ongoing clinical trials are comparing neo-adjuvant chemotherapy followed by concurrent chemoradiation versus chemoradiation alone.

Concurrent chemoradiation delivers combined modality therapy. The benefit is two-fold; chemotherapy may have an effect on regional or distant micrometastasis while at the same time act as a radiation sensitizer. Many chemotherapy agents are used concurrently with radiation, the most common being cisplatin and 5-FU, and schedule and dose can vary depending on physician preference. Several randomized trials and a recent meta-analysis have shown a benefit for local control and survival in patients treated with concurrent chemoradiation compared with radiation alone.[5] The well-publicized Intergroup 0099 trial randomized patients with nasopharynx cancers to standard once-a-day radiation therapy plus or minus cisplatin chemotherapy. The combined treatment arm had a significantly improved disease-free and overall survival of 69% v 24% and 78% v 47% respectively,compared to radiation therapy alone.[7] Another trial performed by the **French Head and Neck Oncology and Radiotherapy Group (GORTEC)** compared standard once-a-day radiation therapy to the same radiation plus concurrent cisplatin and 5-FU. At 5 years the combined treatment was significantly better for local control (48% v 25%), disease-free survival (27% v 15%) and overall survival (25% v 16%).[8]

Several trials have compared altered fractionation schemes to concurrent chemoradiation. The results revealed that the concurrent treatment was better than a variety of altered fractionation protocols. Brizel et al showed that at 5 years follow-up, 70 Gy with concurrent cisplatin and 5-FU was superior to hyperfractionated radiation to 77 Gy radiation alone. Both local control, 70% v 44%, and overall survival, 42% v 27%, were better in the concurrent treatment arm compared to radiation therapy alone.[9] A separate trial compared hyperfractionation with 77 Gy radiation alone to hyperfractionation 77 Gy plus concurrent cisplatin. The results showed that concurrent chemoradiation was better than hyperfractionated radiation therapy alone with a disease-free survival benefit of 24% at 5 years.[10] A German Cancer Society trial combined hyperfractionation and accelerated fractionation, testing this aggressive radiation regimen with and without concurrent chemotherapy.[11] Despite the higher dose and short treatment time on the radiation therapy alone arm, the concurrent chemotherapy again had improved disease-free and overall survival.[11]

From the data, it can be concluded that concurrent chemoradiation is better than conventionally fractionated radiation or intensive altered fractionation radiation therapy schemes for advanced head and neck cancer. While some studies have been performed with altered fractionation and concurrent chemotherapy, there is no agreement as to which radiation therapy fractionation schedule to use or even if concurrent chemotherapy is better with standard fractionation or altered fractionation. Two open trials address these issues; both are nearing their accrual goals. The RTOG is comparing its most effective accelerated fractionation regime, 72 Gy in 6 weeks, plus concurrent cisplatin versus standard once-a-day radiation, 70 Gy in 6 weeks, plus the same concurrent chemotherapy. The French GORTEC group is comparing 3 different fractionation schemes, all with concurrent carboplatin and 5-FU. The arms are standard fractionation, accelerated fractionation (70 Gy in 6 weeks) and markedly accelerated hyperfraction (64.8 Gy in 3.5 weeks).

For patients with a high risk of recurrence after surgery for locally advanced head and neck cancer, post-operative radiation therapy is indicated. The data are mostly retrospective or prospective single arm trials. However, the RTOG dose escalation trial has led to guidelines for dose and target volumes in post-operative radiation therapy.[12] The use of concurrent chemotherapy with post-operative radiation therapy in patients with high-risk head and neck cancer has also been studied. Two randomized trials revealed that concurrent chemoradiation was better than radiation therapy alone in the post-operative setting.[13, 14] Both studies used standard radiation therapy to 66 Gy and concurrent cisplatin. In the RTOG study, patients treated with combined therapy had a significant increase in local and regional control with a failure rate of 18% at 2 years, compared to 28% in patients treated with radiation alone.[13] There was also an increase in disease free survival for the combined therapy arms, but no difference in the overall survival between groups.[13] The European trial had similar results with respect to local control and disease-free survival at 5 year follow-up and revealed an overall survival benefit of 13%.[14]

Toxicity from Combined Modality Therapy

While concurrent chemoradiation increases the efficacy of treatment, it comes at the cost of increased toxicity. A brief review of toxicity data reveals that even the least effective treatment, once-a-day therapy, can result in severe complications. Some of the most complete data comes from the French GORTEC study comparing standard radiation therapy alone versus the same radiation with concurrent carboplatin and 5-FU: during their treatment 71% of the patients in the radiation plus chemotherapy arm had confluent mucositis compared to 39% in the radiation therapy alone arm.[15] Almost all the patients in the combined treatment arm had xerostomia to some degree; 35-45% had grade 3 or 4 dry mouth.[16] Late toxicities were described in several different publications. Depending on the toxicity scoring system, different results were obtained. In a 2003 study, the GORTEC investigators reported

that 82% of patients in the combined treatment arm had one or more grade 3 or 4 late toxicity, compared to 42% in the radiation therapy alone arm.[16] In a separate study in 2004, the same investigators used a different scoring system, which showed 56% of patients in the combined treatment arm with a grade 3 or 4 late toxicity compared to 30% in the radiation therapy alone arm.[17] In both studies the most commonly damaged organ was the salivary gland, resulting in xerostomia and skin damage, resulting in fibrosis.

Because of the large percentage of patients with high-grade side effects, many investigators have been searching to decrease toxicity. Many compounds have been studied with the intent of altering the course of xerostomia, mostly without success. Amifostine, WR-2721, a thiol compound that accumulates in epithelial tissues such as salivary glands,[18] has been found to be effective. In a phase III trial patients receiving standard head and neck radiation therapy were randomized to daily intravenous Amifostine or not.[18] There was significantly less acute xerostomia of >grade 2 in patients receiving Amifostine, 51% , compared to 78% in patients without Amifostine. Long-term xerostomia was also significantly less with Amifostine, 34 %, compared to 57% without Amifostine.[18] Unfortunately there was no improvement in acute mucositis with Amifostine. Amifostine has a small chance of its own toxicity, 5% nausea and vomiting and <1% hypotension. This study was instrumental in the **Food and Drug Administration (FDA)** approval for the use of this drug in patients receiving radiation therapy for head and neck cancers.

One promising compound being tested to reduce both xerostomia and mucositis is a targeted therapy, recombinant human **keratinocyte growth factor (KGF)**.[19] The potential mechanism of action is to stimulate epithelial cell proliferation; phase I and II trials have been underway, and preliminary data suggest a decrease in both xerostomia and mucositis.[19]

A recent technological improvement in the delivery of radiation will also decrease the incidence of xerostomia**. Intensity modulated radiation therapy (IMRT)** is discussed elsewhere in this issue; however, one of its most beneficial applications is in the treatment of head and neck cancer. IMRT allows treatment of tumors to standard (or higher) doses while decreasing the dose to surrounding normal tissues. With IMRT, the physician sets upper and lower limits of dose for specific structures and the computer program attempts to meet these constraints by modulating the intensity of the radiation during the treatment. This can result in what appears to be radiation "bending" around critical structures. In head and neck cancer, this can result in a significant decrease in the dose to one or both parotid glands and other salivary glands and also allows for sparing of the spinal cord in a manner not possible using older techniques. Several studies have revealed that patients with head and neck cancer treated with IMRT had a better quality of life, due to decreased xerostomia.[20,21]

Newer targeted therapies that may lead to radiosensitization may also decrease the toxicity of combined modality therapy while increasing efficacy. Many pathways are under investigation as targets, but **epidermal growth factor receptors (EGFR),** tyrosine kinases and angiogenic pathways have been studied the most.[22] Most of these targets have been through pre-clinical and phase I trials, some in head and neck cancer, with mixed results.[22]

Combined chemotherapy and radiation therapy is the mainstay of treatment of advanced head and neck cancer. Despite this aggressive treatment, local recurrence and distant metastasis are still too common. In addition, the toxicity of these treatments can be significant even with the recent approval of Amifostine for xerostomia. New technological advances, IMRT, as well as targeted therapies, KGF and EGFR antagonists, will hopefully lead to more effective, less toxic therapy for head and neck cancer.

Esophageal Cancer

Approximately 14,000 new cases of esophageal cancers will be diagnosed in the United States this year and almost as many deaths.[23] The incidence of esophageal cancer in the United States has increased over the last several decades. At the same time there have been significant changes in the histology of the disease. In the recent past, squamous cell carcinoma represented the majority of the cases of esophageal cancer. Over the past 20 years, the incidence of adenocarcinomas of the distal esophagus has increased and now likely represents the most common histology in the United States.[24]

Although the etiology of esophageal carcinoma is unknown, cigarette smoking and alcohol intake have been correlated with squamous cell carcinoma and cigarette smoking has been associated with adenocarcinoma.[24] Gastroesophageal reflux disease is also associated with adenocarcinoma of the esophagus: one study estimates an eightfold increased risk.[24] Patients with Barrett's esophagus are at a high risk for the development of adenocarcinoma of the esophagus. It has been calculated that these patients have a 0.5% risk per year of cancer.[24]

Staging of esophageal cancer is performed using the TNM system. The T stage is based on the depth of primary tumor invasion found at surgery therefore preoperative staging is difficult. Tumor staging can be performed with endoscopic ultrasound and nodal staging can be assessed by thoracoscopy.[25] Over half the patients diagnosed with esophageal cancer are unresectable or have metastatic disease at presentation.[24] There does not appear to be any difference in stage at presentation for adenocarcinoma compared to squamous cell carcinoma.[24]

Surgery has been the traditional treatment for early-stage esophageal cancer, but many patients are not candidates for surgery. Most patients with symptomatic esophageal cancer die within three years of surgery and the 5-year survival rate is approximately 5%-15% with over half having a local recurrence.[25] Treatment of patients with radiation therapy alone has led to similar results.[24] Consequently, there have many investigations into chemotherapy and radiation therapy as adjuvant treatments.

Combination chemotherapy and radiation therapy for esophageal cancer

A number of trials have compared radiation alone versus chemoradiation for unresectable esophageal cancer. The most quoted is an RTOG protocol that randomized patients to cisplatin, 5-FU and 50 Gy radiation or to 64 Gy radiation alone.[26] The results reveal a benefit in survival for patients receiving combined treatment versus radiation alone, 38% v 10% at 2 years and 27% v 0% at 5 years respectively.[26] A trial also assessed the benefit of escalating the radiation dose with combined modality because the doses in the previous study were not the same. Patients were randomized to 50.4 Gy or 64.8 Gy with the same chemotherapy, cisplatin and 5-FU.[27] There was no difference in overall survival or local control between the high-dose or the standard dose arms, 31% v 40% for 2-year survival and 44% v 48% for local control respectively.[27] The conclusion was that standard therapy for unresectable esophageal cancer is 50.4 Gy with concurrent chemotherapy.[27]

Given the relatively poor results of surgery alone for patients with respectable disease, studies have tested a variety of neo-adjuvant treatments. Pre-operative radiation therapy alone has been has been tested multiple times, with no demonstrated benefit.[24] Pre-operative chemotherapy alone showed no significant benefit.[24]

Several randomized trials have compared combined chemoradiation prior to surgery versus surgery alone for resectable esophageal cancer. These trials enrolled patients at various times between 1983 and 1995; most comprised patients with squamous cell carcinoma. Only one of the studies revealed a survival benefit and it differed from the others in that it enrolled only patients with adenocarcinomas.[28] Of note was that patients with a complete response to chemoradiation therapy appeared to have a better outcome.[29] Despite these trials, combined modality neo-adjuvant therapy is widely used. Given the contradicting data, three separate meta-analysis have further investigated neo-adjuvant chemoradiation.[30,31,32] One meta-analysis suggested that there was an advantage for neo-adjuvant chemoradiation in 3-year survival and local control.[30] Another meta-analysis showed that neo-adjuvant chemoradiation correlated with a reduction in 3-year mortality, however, post-operative mortality increased in patients who receive chemoradiation.[31] The most recent meta-analysis did not report any statistical advantage for neo-adjuvant chemoradiation, compared to surgery alone.[32] This study did show a non-significant advantage in survival for combined modality therapy.[32] The most interesting aspect of these meta-analysis is that they, for the most part, evaluated the same randomized trials. There are many criticisms of the initial randomized trials. Presently many new radiosensitizing chemotherapeutic agents are being tested in the hope of increasing the local control and survival in patients with respectable esophageal cancer. In addition, many of the targeted therapies discussed above in respect to head and neck cancer are also being tested in esophageal cancer.

For the present time, most patients with unresectable esophageal carcinoma are treated with combined chemotherapy and radiation therapy. Patients with respectable disease are likely to be treated with neo-adjuvant chemoradiation, despite the lack of strong category 1 evidence. These patients should be considered candidates for protocols evaluating newer chemotherapies and targeted agents as part of a neo-adjuvant approach to respectable esophageal carcinoma.

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The Role of Palliative Radiation in the Management of Brain, Spinal Cord, and Bone Metastases

Nicklas B.E. Oldenburg, MD

In the field of radiation oncology, much of our research has focused on organ preservation, improving local control, and reducing the toxicities of treatment. Nevertheless, an estimated 40-50% of cancer patients treated with radiation therapy are treated with palliative intent.[1,2] Radiation is a safe and effective method of palliating a variety of emergent and non emergent clinical situations. This review will discuss the treatment options for the patient presenting with brain metastases, summarize the effectiveness of these treatments, review the potential side effects, and propose a treatment algorithm to help clinicians manage patient with brain metastases.

Brain Metastases

Brain metastases from cancers of other sites are the most common intracranial malignancy, with an annual incidence of greater than 170,000. [3] Twenty-five to 50% of cancer patients will develop spread to the central nervous system at some point in their disease.[4] The most commons malignancies to metastasize to the brain are lung (48%), breast cancer (15%), melanomas (9%), colorectal cancer (6%) and other known primaries (13%). [5]

Table 1 lists the most common presenting signs and symptoms of brain metastases.[6] Cognitive changes, hemiparesis, and headache are frequently noted. Most patients with brain metastases have baseline neurocognitive deficits. Concerns regarding treatment related morbidities must be weighed against baseline deficits.

Table 1: Signs and Symptoms in Patients Presenting with Brain Metastases

Signs	Symptoms
Hemiparesis (59%)	Headache (49%)
Cognitive problems (58%)	Mental Problems (32%)
Hemisensory loss (21%)	Focal Weakness (30%)
Papilledema (20%)	Ataxia (21%)
Ataxia (19%)	Seizures (18%)
Apraxia (18%)	Speech Problems (12%)

Table 2: Factors Predicting for Improved Survival following Whole Brain Radiation

Age <65
Karnofsky Performance Status >70
Control or absence of primary tumor
Absence of extracranial systemic metastatic disease
Single brain metastasis

Approximately 20% of patients present with a solitary brain metastasis; 80%, with two or more lesions.[7] Untreated, the median survival for patient with brain metastases is 4 weeks. High dose corticosteroids increase survival to two months. **Whole brain radiation therapy (WBRT)** increases the median survival to 3-6 months, with 15% 1-year survival and 5-10% 2-year survival. [8,9,10]

Table 2 shows factors demonstrated to predict for improved survival in patients treated with WBRT. [11] Not every patient benefits equally from palliative radiation to the brain. Those patients with significant metastatic disease, Karnofsky Performance Status (KPS) ≤60, and limited ambulation have a median survival of 30 days. Those with widespread metastatic tumor, KPS ≤50, and whose ambulation is limited to sitting have a median survival of 20 days. [12] In these patients, supportive care and hospice should be considered as an alternative to radiation. Patients with good performance status, minimal or absent systemic disease, and one or few brain lesions have a median survival of ten months. [13]

The Management of Multiple Brain Metastases

The standard treatment for patients with multiple brain metastases is dexamethasone (4-6 mg four times daily) to reduce swelling, and external beam WBRT initiated 12-24 hours later. Usually 30 Gy of radiation is delivered in 10-12 fractions through opposed lateral fields. This regimen is based on data from four prospective randomized **Radiation Therapy Oncology Group (RTOG)** trials, which enrolled more than 1650 patients and compared 12 different radiation doses and treatment schedules. [14, 15, 16] Regimens that were compared included 30 Gy in 2 weeks, 30 Gy in 3 weeks, 40 Gy in three weeks, and 40 Gy in 4 weeks. All the studies were equivalent with respect to response (70-90%), neurological improvement (60%) and survival (3-6 months).

The Role of Surgery in the Management of Brain Metastases

Patients with three or fewer brain metastases and good performance status may be candidates for surgical resection, external beam radiation, and/or stereotactic radiation.

Despite extensive research, there remains controversy as to the optimal regimen for these patients. Roy Patchel and colleagues from the University of Kentucky have published several important randomized trials on the management of patients with *solitary* brain metastases.[9, 17] They compared surgical resection of the single metastasis followed by WBRT (36 Gy in 12 fractions) to WBRT alone. The local recurrence (20% versus 52%), functional independence (9.5 months versus 2 months), and survival (10 months versus 3.75 months) were improved in the surgery and WBRT

arm versus the WBRT alone arm. A second randomized trial from the Netherlands confirmed improved survival ((10 versus 6 months) in the combined surgery and WBRT (40 Gy in 20 fractions) compared to WBRT alone.[18] Those patients with active extracranial disease had equivalent survivals of five months. A third randomized trial[19] failed to show any survival benefit (6.3 months versus 5.6 months) to adding surgery to WBRT in patients with solitary brain metastases. Forty five percent of patients in this trial had extracranial disease and 21% had KPS<70. These patient characteristics may explain why no survival advantage was seen in this trial. In summary, surgical resection of solitary brain lesions followed by WBRT appears superior to WBRT alone in patients with good KPS and stable extracranial disease.

Patchel and colleagues published a second trial[17] which compared surgery alone for solitary brain metastases to surgery followed by WBRT (50.4 Gy in 28 fractions). Post operative WBRT improved local recurrence (10% versus 46%), other intracranial recurrence (14% versus 37%), death due to neurological symptoms (14% versus 44%), but did not improve overall survival (48 weeks versus 43 weeks). In a retrospective analysis[20] of 229 patients, Smalley and colleagues found the median survival to be 15 months for those who had post operative WBRT compared to 8 months for those undergoing resection alone.

The Role of Radiosurgery in the Management of Brain Metastases

Stereotactic radiosurgery (SRS) and gamma knife radiosurgery (Gamma Knife) have been extensively investigated in patients with brain metastases. Many retrospective trials demonstrate tumor response rates to radiosurgery.[21, 22] SRS delivers a single fraction of high dose of radiation through multiple geometric positions using a modified linear accelerator. Gamma Knife uses a Cobalt [60] source machine to deliver the single high dose fraction of radiation. Radiosurgery, a less invasive substitute for surgical resection, is relatively easy to administer and can treat tumors in areas of the brain that are difficult or impossible to resect. Radiosurgery may decrease neurosurgery-related and radiation-related side effects.

What role does radiosurgery play in the management of patient with three or less brain metastases? Options include radiosurgery alone (or with delayed WBRT for failure), WBRT followed by radiosurgery, or surgical resection followed by radiosurgery. Sneed and colleagues[23] published a multi-institutional trial comparing radiosurgery alone to WBRT followed by radiosurgery. 10 institutions contributed data from 983 patients with newly diagnoses brain metastases treated with radiosurgery. 569 patients met the criteria of radiosurgery alone (268) or radiosurgery given within one month of the WBRT (301). Patients were analyzed by Radiation Therapy Oncology Group (RTOG) **recursive partitioning analysis (RPA)** Class 1 (age <65 years and KPS ≥70 and no extracranial disease) vs. Class 2 (KPS ≥70 but age ≥65 years and/or extracranial disease present) vs. Class 3 (KPS <70).[11] Median survival was 14 months for radiosurgery and 15.2 months for WBRT and radiosurgery for RPA Class 1, 8.2 vs. 7 months for Class 2, and 5.3 vs. 5.5 for Class 3. After adjusting for RPA class, there was no difference in overall survival between radiosurgery alone and WBRT followed by radiosurgery. Patients treated with radiosurgery, however, were five times as likely to require salvage brain treatment as those treated with WBRT and radiosurgery.

The Sneed study did not address whether radiosurgery added anything to WBRT alone. Three randomized trials have addressed this issue. A small randomized trial compared 13 patients treated with WBRT (30 Gy in 12 fractions) with 13 patients who received WBRT followed by SRS boost (a tumor margin dose of 16 Gy).[24] All patients had KPS >70, two to four brain lesions, and all lesions were <2.5 cm. The study was stopped at 60 % accrual after interim analysis. Local failure at one year was 100% in the WBRT arm and 8% in the WBRT plus SRS arm. Median survival was 7.5 months in the WBRT alone arm and 11 months in the combined treatment arm. The two year overall survival was 0% in the WBRT arm and 20% in the WBRT plus SRS arm.

Based on these intriguing, albeit small patient numbers, the RTOG performed a phase III randomized trial of WBRT with or without SRS boost for patient with one to three brain metastases.[25] 333 patients from 55 institutions were treated with either WBRT (37.5 Gy in 15 fractions) or WBRT followed by a SRS boost (15-24 Gy). Patients were stratified by number of metastases and status of extracranial disease. Primary outcome was survival, with secondary outcomes of local tumor control, performance measurements, and overall intracranial recurrence rates. A statistically significant survival advantage was noted in patients with a solitary brain metastasis who received combination treatment with WBRT and SRS boost (6.5 months vs. 4.9 months, p=0.039). In addition, 47% of patients receiving a SRS boost had a stable or improved KPS six months after treatment, compared to 27% in the WBRT alone arm. By multivariate analysis, the was a survival advantage to combined therapy in RPA Class I patients (p=<0.0001).

In a third randomized trial by Chougule and colleagues at Brown University (published in abstract form only),[26] 96 patients were randomized to three arms: 36 patients received gamma knife radiosurgery alone (30 Gy), 31 patients WBRT alone (30 Gy in 10 fractions), 37 WBRT with gamma knife boost (30 Gy + 20 Gy boost). Researchers found no survival differences between the three arms. Local control was improved in patients receiving gamma knife, but those patients were twice as likely to develop new brain metastases. A major confounder to this study was the fact that 53% of the patients underwent resection of a large, symptomatic lesion prior to randomization. Surgery improved overall survival in this study regardless of treatment group, but showed no advantage for those who received surgery and gamma knife.

Late side effects of Radiation Therapy to the Brain

A review of the role of radiation in treating brain metastases would not be complete without a discussion of the late sequelae of therapy. There is a generalized fear that WBRT will result in horrendous late side effects. Much

of the supporting data, though, come from the pediatric radiation literature and are not necessarily applicable to adult brains. There have also been many neurocognitive studies of glioma patients treated with radiation. It is probably not fair to compare this primary, infiltrate brain lesion with brain metastases because radiation doses, treatment fields, and the extent of surgery are all different.

In an often cited article on the late effect of palliative WBRT, DeAngelis at Memorial Sloan-Kettering[27] reported on 47 patients alive without brain recurrence 12 months following WBRT. Five patients (11%) had dementia, but they all received non conventional radiation treatment. Four of the five had daily treatment fractions of 5 Gy to 6 Gy, or roughly twice what is considered the standard dose. The fifth patient received the conventional 3 Gy daily fraction size, but with a concurrent radiosensitizer. Daily radiation fraction size clearly affects late side effects in some tissues, including brain.[28] Zero of 15 patients who received less that 3 Gy per fraction of WBRT had dementia. These data would argue that large daily radiation fraction size, and not WBRT itself, may lead to dementia or other severe late side effects. Even if one accepted the 11% dementia rate, only 15% of patients treated with WBRT are alive at one year. [8,9,10] That means that, at most, only 1.5% of patients alive at one year WBRT would develop dementia. Most patients treated with conventional WBRT are never going to develop severe late effects from their treatment. Long-term survivors may develop subtle neurocognitive changes not easily detected by bedside testing, but this must be weighted against the effects of not treating the patients with WBRT.

Radiosurgery is often advocated as a treatment option to avoid or delay WBRT: 37-63% of patients treated with SRS as monotherapy will require salvage brain treatment.[7] In these retreated patients there is 5% radiation necrosis incidence requiring craniotomy. [7] The neurocognitive impact of retreatment plus or minus additional surgery are not well studied, but probably more worrisome than that of WBRT alone.

Conclusions Regarding the Management of Brain Metastases

So, how should the patient with brain metastases be managed? Figure 1 proffers a treatment algorithm based on number of metastases, performance status, and respectability (when applicable). As discussed in this review, controversies such as upfront versus delayed WBRT following radiosurgery, exist. Clinical judgment and patient preference will dictate treatment decisions.

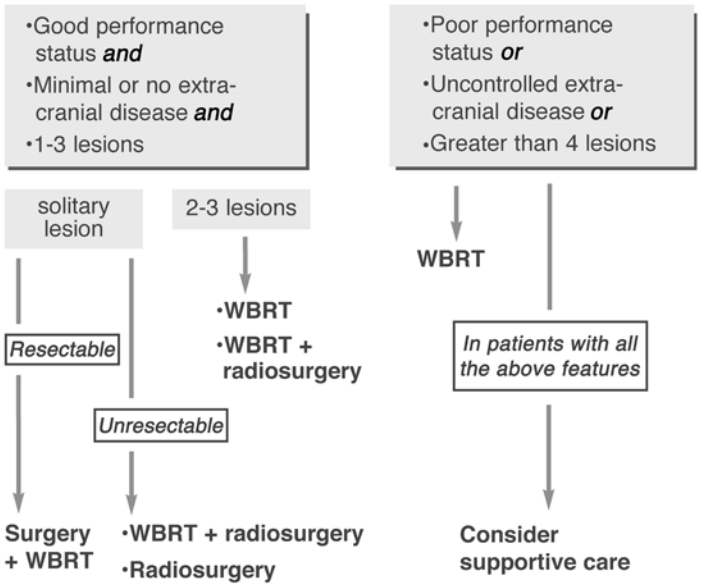
Metastatic Disease to Bone

The metastasis of tumors to bone is common with advanced disease. Many tumors preferentially deposit in bone compared to other body sites. Sixty-five to 75% of patients with bone metastases will experience pain and or impaired mobility.[29] In addition, bone metastases can cause fracture, decreased marrow production, or spinal cord or nerve root compression. Bone is a dynamic structure, consisting of bone cells (osteoclasts, osteoblasts, and osteocytes), hematopoietic cells, and immune cells.[30] Approximately 10% is replaced every year.[31] Tumor cell metastasis disturbs this normal balance of osteoclastic and osteoblastic processes.

While there are various methods by which tumor metastases can involve the bone, the most common and important route is hematogenous spread.[32] TGF-β IGFs and other products of bone resorption may serve as chemotactants for tumor cells. [29] Once present in bone, tumor cells activate osteoclast-mediated osteolysis, which induces growth factors that stimulate osteolytic cytokines, leading to osteolysis. [33] In addition to osteolysis, there is new bone formation. Reactive bone formation is the most frequent form of bone healing in the presence of metastases. This process is identical to that for bone fracture from trauma. The bone that forms in the presence of metastases lacks the strength of normal lamellar bone, and has affinity for bisphosphonate and polyphosphate. This avidity for bone seeking molecules is the basis for bisphosphonate therapy in patients with hypercalemia and bone metastases.[34]

Regular physical examination and diagnostic imaging are important for the early detection of bone metastases. Plain film radiographs, computed tomography studies, bone scans, and magnetic resonance imaging scans can all assist in making the diagnosis. Appropriate medical analgesia and palliative radiation therapy are common treatments for the management of symptomatic bone metastases. Surgical intervention

Figure 1: An Algorithm for Radiotherapeutic Management of Patients with Brain Metastases



is usually restricted to stabilization of a pathologic fracture, or prophylactic surgery to prevent fracture in a lesion involving a weight-bearing bone.

Management of Bone Metastases with External Beam Radiation Therapy

Bone metastases respond well to radiation therapy. Many randomized trials have compared pain relief among different radiation dose fractionation regimens. All the randomized trials between 1966 and 2001 were combined into a recent meta-anaylysis.[35] Some trials compared single versus single fraction sizes, other trials single versus multiple fraction regimens, and yet other different multiple fraction regimens. Single fraction doses varied from 4-10 Gy per fraction. Multifraction regimen included 20-25 Gy in 5 fractions, 30 Gy in 10-15 fractions, 15 Gy in 3-5 fractions, and 24 Gy in 4-6 fractions. The median dose for the multifraction radiation regimens was 20 Gy in 5 fractions with a range of 20 Gy in 5 fractions to 30 Gy in 10 fractions. There was no statistical difference in complete pain response between the treatment regimens. A complete response was achieved in 33.4% of the patients who received single fraction radiation and 32.3% of patients receiving multifraction radiation. The overall response rates for evaluated patients were also similar for the single versus multifraction radiation regimens(72.7% versus 72.5%). No dose response relationship could be demonstrated.

United States physicians have been cautious about large single fractions of radiation because of potential increased acute and late side effects. Our standard palliative radiation dose is 30 Gy in 10-12 fractions. Recently the RTOG published a randomized phase III trial comparing 8 Gy in one fraction to the 30 Gy in 10 fractions in patient with painful bone metastases from breast or prostate cancer.[36] A total of 949 patients were enrolled and 898 were eligible and analyzable. Results are summarized in Table 3. Both regimens had equivalent pain and narcotic relief at 3 months with 33% of patient no longer needing narcotics. There was more grade 2-4 acute toxicity in the 30Gy arm, but a higher rate of retreatment in the 8 Gy arm. Overall both regimens were well tolerated with few side effects.

Management of spinal cord metastases

Spinal cord compression is an emergent medical condition that can lead to irreversible loss of neurologic function. The accurate and rapid diagnosis is key to the prevention or reversal of paralysis.

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Table 3.

RTOG 97-14: 8 GY in 1 fraction vs. 30 Gy in 10 fractions

Fractionation	Number patients	CR	PR	Acute Toxicity	Late Toxicity	Pathologic Fracture	Retreatment Rate
8 Gy X 1	445	15%	50%	10%	4%	5%	18%
3 Gy X 10	443	18%	48%	17%	4%	4%	9%(p=0.001)

Abbreviations: CR, complete response; PR, partical response

PREOPERATIVE TREATMENT OF RECTAL CANCER

SCOTT A. TRIEDMAN, MD

In 2003, there were approximately 42,000 new cases of rectal cancer and 8,500 rectal cancer deaths in the United States. In 2005, in Rhode Island, there will be an estimated 250 cancer deaths from colorectal malignancies.[1] Surgery remains the mainstay of therapy as the primary curative modality for the treatment of rectal cancer. Unfortunately, in spite of complete removal of the tumor, a substantial percentage of patients will relapse and die of recurrent disease. As a result, a great deal of effort has been focused on the development of adjuvant treatment strategies for this disease while also trying to maintain quality of life and specifically, to preserve continence.

POSTOPERATIVE RT

The treatment of rectal cancer has advanced since Miles initially described the **abdominoperineal resection (APR)** in 1908.[2] For several decades, this remained the standard of care for all resectable rectal cancers. Over time, surgical approaches evolved. By the 1970s, the **low anterior resection (LAR)** was widely accepted for proximal and mid-rectal cancers. Unfortunately, even with improvements in surgical techniques and refinements of surgical approach, the risk of recurrence remained unacceptably high following surgery alone in patients with Stage 2 and 3 rectal cancers. For patients with T1-2NOMO disease the incidence of local failure as a component of failure is less than 10%. The incidence increases to 15 to 35 % in stage T3NOMO and rises to 45% to 65% in stages T3-T4N1-2MO. [3, 4, 5, 6]

"...THE RECENT DATA SUGGEST A POSSIBLE BENEFIT TO PREOPERATIVE CHEMORADIOTHERAPY..."

In one landmark study Gunderson and Sosin at the University of Minnesota evaluated the pattern of local nodal and distant failure after curative rectal cancer surgery in a series of second-look operations.[6] This report as well as subsequent studies defined the most common sites of locoregional recurrence to include the presacral space, anastomosis or the perineum (in APR patients). Less common sites may include bladder or pelvic nodal stations. Other studies demonstrated that certain pathologic factors including the depth of tumor invasion and lymph node involvement can influence tumor recurrence rates.[7] These studies were crucial in providing the rationale for postoperative therapy and assisted in determining which patient groups might benefit from postoperative pelvic radiation.They also helped to define the anatomic extent of radiation treatment portals in the early postoperative adjuvant trials.

Unfortunately, while postoperative **radiation therapy (RT)** alone was demonstrated to improve local control, a number of trials failed to demonstrate any improvement in overall survival.[8, 9] Given the initial success with 5-FU-based chemotherapy for colon cancer, subsequent rectal cancer studies looked at postoperative adjuvant chemotherapy either alone or in conjunction with postoperative RT. The Gastrointestinal Tumor Study Group randomized patients with Stage 2 and 3 rectal cancer to four different regimens, including: no adjuvant therapy, radiation therapy alone, 5-FU-based chemotherapy alone or chemo-radiation.[10] The local recurrence rate was 10.8% for chemo-radiation patients versus 24.1% for no therapy. There was also reduction in local failure in the chemo-radiation group compared to the RT alone group (10.8% versus 20%, respectively). The greatest difference in outcome was seen when comparing the combined therapy group and the surgery only arm. Survival was improved in the combined modality group (54% vs. 27 %, p=.05).[11]

In 1990, a National Cancer Institute Consensus Conference concluded that combined modality therapy was the standard postoperative adjuvant treatment for patients with T3/T4 or N1/N2 disease.[12] Subsequent studies tried to improve on these results and confirmed the benefit of adjuvant chemo-radiation on local control and overall survival.[13]

In 1994, a North Central Cancer Treatment Group trial demonstrated that a prolonged continuous infusion of 5-FU during postoperative RT both decreased local tumor failure and improved survival compared to bolus 5-FU during radiation as a component of sequential combined modality postoperative adjuvant therapy.[14] Because of these successes, and improvements in the adjuvant therapy of colon cancer, more intense 5-FU based regimens were studied with the hope that they would show improved efficacy in the treatment of locally advanced rectal cancer. Unfortunately, this benefit was not demonstrated in subsequent trials.[15] With the newer chemotherapeutic agents such as irinotecan and oxaliplatin there has been renewed enthusiasm and effort in developing alternative systemic strategies in combination with adjuvant radiation.

PREOPERATIVE RT

Over the last decade, there have been many attempts to improve the efficacy and reduce the toxicity of adjuvant therapy in rectal cancer. One management approach that has gained attention has been to utilize preoperative chemo-RT in the neoadjuvant setting prior to definitive surgery. While it remains unclear whether a preoperative or a postoperative treatment approach is optimal in Stage II and III rectal cancer, proponents of a preoperative approach have been gaining momentum; but relatively few studies have compared these two forms of therapy in randomized con-

trolled clinical trials. Part of the difficulty in evaluating preoperative RT has been the different treatment fractionation schemes used in some of the European trials compared to trials in the United States. A number of studies from Europe have utilized a hypofractionated RT schedule (500 cGy for 5 treatments) followed by immediate surgery. This contrasts with the "standard", conventionally fractionated course of irradiation in the US to a dose of approximately 5000 cGy at 180-200 cGy per fraction over 5 to 5.5 weeks followed by surgery 4-8 weeks later. While both these preoperative regimens appear to improve local tumor control, the more protracted course allows more time for tumor shrinkage before surgery, which is likely to increase the chance of sphincter preservation in patients with low-lying rectal tumors. In the short course preoperative regimen, it remains unclear how to best incorporate adjuvant chemotherapy into a hypofractionated preoperative radiation treatment plan.

There are a number of theoretical reasons why preoperative RT may be beneficial. In the preoperative settings, the tissues are well oxygenated and more likely to be sensitive to the tumoricidal effects of RT compared with the often more poorly vascularized tissue associated with scar after surgery. In addition, before surgery, the small bowel can often be successfully mobilized out of the radiation treatment portals through patient positioning and bladder filling. In contrast, after surgery, adhesions may prevent adequate small bowel mobilization resulting in larger volumes of small bowel within the treatment field. In those patients who require an APR, postoperative radiation fields typically will include coverage of the perineum in order to reduce the risk of recurrence in these surgically manipulated tissues. This perineal coverage may result in significantly greater acute skin toxicity. In the preoperative setting, the perineum is typically not with the radiation treatment field. Finally, with preoperative treatment, unirradiated colon is used for the anastomosis, which may allow for improved healing. In addition, much of the irradiated bowel is removed at the time of surgery following preoperative RT.

PREOPERATIVE RT TRIALS

Preoperative therapy for rectal cancer has been the preferred treatment strategy in Europe for many years. The first randomized trial of preoperative radiation to demonstrate a benefit was the Swedish Rectal Cancer Trial.[16] In this phase III trial, patients were randomized to either an intensive short course of preoperative radiation (25 Gy in 5 fractions) followed by surgery one week later or to a surgery alone control arm. At 5 years of followup, there was a significant reduction in local recurrence rates in the preoperative irradiation group versus surgery alone (11% vs 27%, $p<0.001$). Reduction in local failure was found in patients with all stages of disease. There was no impact of adjuvant irradiation on distant metastases; however, the patients in the preoperative radiation group demonstrated improved survival. It should be noted that in the Swedish study, patients did not undergo **total mesorectal excision (TME).** TME requires a more complete resection of the mesorectal tissues in order to clear adjacent lymph nodes and also to adequately manage the radial margins of the rectal tumor. Theoretically, TME reduces the likelihood of residual tumor cells and may result in improved local control.

In another study the Dutch Colorectal Cancer Group randomized 1805 patients with clinically resectable Stage I-IV rectal cancers to TME alone versus preoperative RT + surgery.[17] The same short course of preoperative RT was utilized as in the Swedish study (5 Gy x 5/fractions). There was strict attention to both surgical and pathology quality control. The early results of this study demonstrated a reduction in the local recurrence rate at 2 years in the preoperative radiation arm from 8.2% to 2.4%, $p<0.001$. There was no improvement in overall survival. Of particular interest, the Dutch trial suggested that there may be subsets of patients in whom TME alone is adequate for obtaining good pelvic control (T1-2, N0 tumors and some node-negative proximal rectal cancers). It should be noted; however, that TME can result in significant complications. In the Dutch trial, a 29% of patients had perineal wound complications rate in patients who received preoperative radiation + TME.[18]

As noted, the rationale for preoperative therapy is not only to improve pelvic control and survival but also to decrease rectal tumor volume, with the goal to increase the likelihood of sphincter preservation. In the Dutch trial where the interval between preoperative RT and surgery was 1 week, there was no down-staging.[19] Generally, when the goal of preoperative therapy includes sphincter preservation, a more protracted course of radiation (45-50.4 Gy at 1.8 Gy/fraction) followed by an interval of 4-7 weeks before surgery seems preferable. This appears to allow for a.) sufficient recovery from the acute side effects of chemo-RT and b.) adequate time for tumor down-staging. Toxicity does not appear to be increased in patients who have delayed surgery.[20]

Three large randomized trials have compared local control and survival in rectal cancer patients treated with preoperative versus postoperative chemo-radiation. Two of these trials were attempted in the United States: NSABP RO3 and GI Intergroup 0147. Both were closed prematurely due to inadequate accrual and were underpowered to detect any survival benefit.[21] Nevertheless, there was important information that was obtained regarding clinical downstaging with preoperative therapy.

In the NSABP R-03 Phase III trial, the study was designed to evaluate optimal timing of chemo-radiation. Patients who were randomized to the preoperative arm received: 1 cycle bolus 5-FU/Leucovorin, 2 cycles of 5-FU/Leucovorin with concurrent radiation therapy (4500 Gy) then surgery followed by 4 additional cycles of 5-FU/Leucovorin. The postoperative group received the same regimen but all therapy was delivered following surgery. When patients were first seen, the surgeons were asked what sur-

gical procedure they thought would be required for both the preoperative and postoperative group patients. In the patients randomized to immediate surgery and postoperative chemo-RT, the initial assessment of the operation required correlated well with the actual operation performed. In patients who received preoperative chemo-RT, sphincter preservation was achieved in 50% of patients, compared to 33% of those who had initial surgery.[22] Also, patients who achieved a complete pathologic response at surgery had an improved survival at 3 years compared to patients with a partial response or stable disease (100% vs 95% vs 83%, p= .02).[23]

The most important information comparing the efficacy of preoperative versus postoperative combined modality therapy comes from the trial by Sauer and colleagues of the German Rectal Cancer Group.[24] Patients with T3 or T4 or node positive rectal cancer were randomly assigned to either preoperative chemoradiotherapy (n=421) or postoperative chemoradiotherapy (n=402). Endorectal ultrasonography was a necessary staging procedure. All surgeons performed mesorectal excisions. The preoperative regimen, completed 6 weeks prior to surgery, consisted of 5040 cGy at 180 cGy per fraction and continuous infusion 5-FU during weeks one and five of radiotherapy. A month following surgery, patients in both study groups received four, 5-day cycles of Fluorouracil. The chemoradiotherapy regimen in the postoperative treatment group was the same except for the delivery of a boost of 540 cGy.

The primary endpoint was overall survival; however, important secondary endpoints included local recurrence rate, colostomy free survival, and long-term complications. The 5-year survival rates were comparable: 76% in patients randomized to chemoradiotherapy and 74% in patients randomized to the postoperative arm (p=.80). Local recurrence, however, was less in the neoadjuvant group (13% vs 6%, p=.006). In addition, there was a reduction in Grade 3 or 4 acute toxic effects in the preoperative treatment group (27% versus 40%, p=0.001). Rates of late toxicity were also reduced in the preoperative arm (14% versus 24%, p=.01) including a decrease in chronic anastomotic stenosis.

The ability of the preoperative treatment to downstage rectal cancer was assessed. At study entry, surgeons determined whether or not a sphincter-preserving operation could be performed. It was predicted that of the 415 patients in the neoadjuvant arm, 116 would require abdominoperineal resection. After neoadjuvant treatment, 39% of these 116 patients did not require a colostomy. In contrast, 19% of 78 patients predicted to require abdominoperineal resection who went directly to surgery had a sphincter-sparing approach. Overall, while this study did not show a survival benefit to the preoperative approach, it suggests that preoperative chemoradiotherapy confers improved local control and reduces both acute and long-term toxicity compared to postoperative chemoradiotherapy.

In conclusion, the recent data suggest a possible benefit to preoperative chemoradiotherapy compared with postoperative treatment. Overall objective response to chemoirradiation is approximately 60-70% with pathologic complete responses of about 15-25% when utilizing 5-FU-based chemotherapy and conventionally fractionated treatment schemes (4500 - 5000 cGy).[25] Future research is seeking to improve local control and survival with newer agents such as Irinotecan and Oxaliplatin. In addition, inhibitors of **vascular endothelial growth factors (VEGF)** such as Bevacizumab are being studied in rectal cancer and ultimately may be integrated into neoadjuvant chemoradiation programs. Other research avenues have included the addition of Amifostine to chemoradiation with the hope of ameliorating the toxicity of chemoradiation. Finally, advances in the technical aspects of image-based radiation treatment planning may ultimately allow for more precise delivery of high dose radiation treatment while at the same time minimizing normal tissue toxicity.

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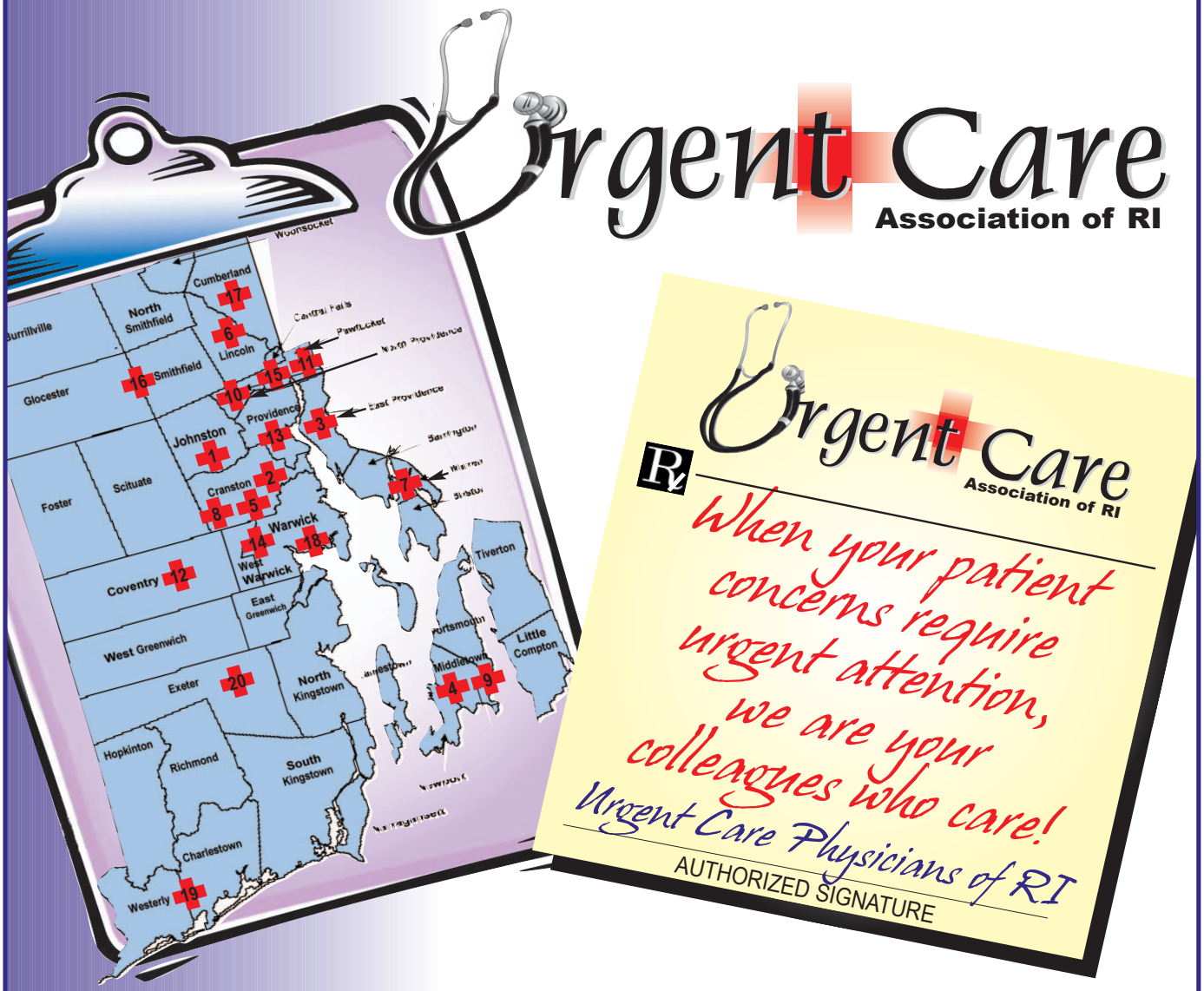

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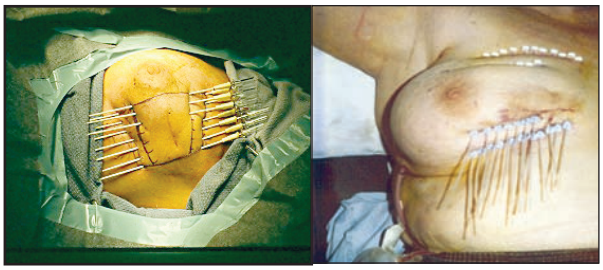
Accelerated Partial Breast Irradiation: Current Modalities and Investigations

Seth A. Kaufman, MD, Thomas A. DiPetrillo, MD, and David E. Wazer, MD

Traditional breast conserving therapy for early stage breast cancer has involved tumor lumpectomy followed by radiation treatment to the entire breast. Prospective randomized data with 20 years of follow-up show this regimen to have similar efficacy to mastectomy, both in terms of local control and overall survival, for patients with early stage node negative disease.[1,2] This regimen involves once daily treatment, five days a week, for 6-6½ weeks. For patients living in remote locations or with other medical conditions that make travel difficult, this can be a prohibitive requirement, ruling out the option of breast conservation. In addition, certain anatomical constraints (such as a large breast) can make delivering a uniform radiation dose to the entire breast difficult. The result is an increased risk of skin and subcutaneous toxicity, both in the short term and in terms of ultimate cosmesis. For these reasons, the option of partial breast irradiation has been gaining attention. Because a relatively small volume of subcutaneous tissue is targeted, the overall treatment time may be shortened to one week without any theoretical increase in long-term toxicity. In addition, the concern for uniform dosing across a large volume of tissue is removed. Several modalities of **accelerated partial breast irradiation (APBI)** are in clinical use. These modalities are being studied in a national prospective randomized trial (NSABP B39/ RTOG 04-13).

APBI challenges the notion that the entire breast is at equal risk for disease recurrence. Evidence from the literature, both in terms of clinical data and pathologic specimen analysis, indicates the region of highest risk for microscopic residual disease and in-breast recurrence is within 1-2cm of the surgical bed.[3-8] Either temporary placement of radioactive sources within the breast (brachytherapy) or highly sophisticated means of conformal external beam radiotherapy can be used to treat volume at risk while minimizing the dose to the surrounding breast. Institutional data have indicated similar efficacy to whole breast radiotherapy both in terms of local control and overall survival. Both the **American Brachytherapy Society (ABS)** and the **American Society of Breast Surgeons (ASBS)** have adopted specific criteria for patient eligibility for APBI. (Table 1) With slight differences, both organizations have limited eligibility by age, margin status, histology, tumor size, and axillary nodal status. Most successful APBI trials have adhered to a size limit and a negative surgical margin status. Restrictions based on age, histology, and nodal status, have not shown consistent correlation with successful results in APBI trials. Nevertheless, the conservative approach of both the ABS and ASBS is justified until long-term local control data become available.

The techniques employed for APBI include multi-catheter interstitial brachytherapy, balloon-tipped catheter brachytherapy, intraoperative brachytherapy, and **three-dimensional conformal external beam radiation therapy (3D-CRT)**. Typical fractionated treatment regimens are either 3.4Gy twice daily over 5 days for a total dose of 34Gy or 4Gy delivered twice daily for 4 days to a total dose of 32Gy. Intraoperative radiation is given in a single dose, which varies depending on the type of radiation. Each method has been studied in single and multi-institutional settings, and each has its own merits in terms of the degree of invasiveness, duration and timing of treatment, and technological requirements.



A B

Figure 1: Multi-catheter interstitial APBI at the time of placement (A) and during radiotherapy (B).

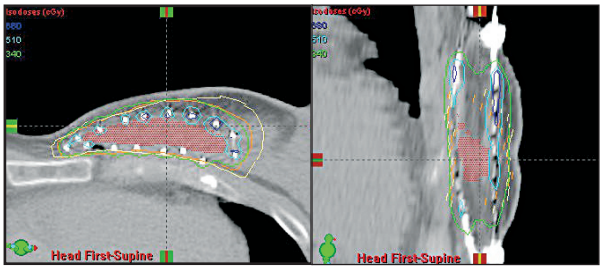


Figure 2: Dosimetric analysis of multi-catheter interstitial APBI.

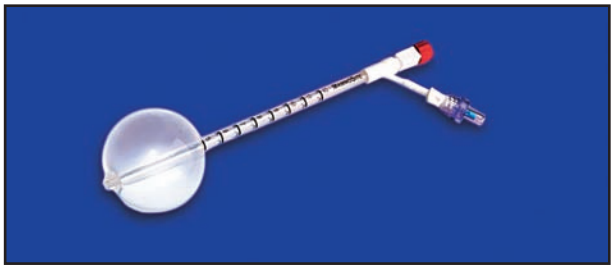


Figure 3: MammoSite radiation therapy system for APBI.

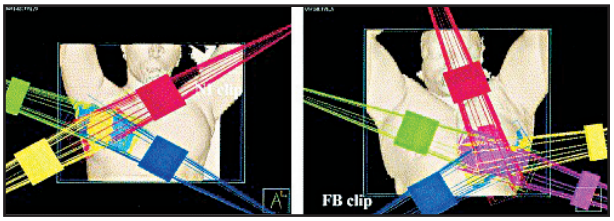


Figure 4: APBI using three-dimensional conformal radiation therapy (3-D CRT).

Work done at our institution and by others helped

to pioneer the multi-catheter technique, the oldest form of APBI. Following surgical excision of the tumor, several small catheters are placed transcutaneously throughout the treatment volume. (Figure 1) Uniform spacing between catheters (typically 1.0-1.5cm) is used for homogeneous dosing (Figure 2), and between 14 and 25 catheters are usually required. Newer techniques of image-guided placement utilizing CT, ultrasound, or stereotactic mammography further ensure the accurate placement and spacing of the catheters. Precise post-placement imaging permits dosimetric calculations of the ideal source positions and durations of placement. Treatment has been prescribed in both a **low dose rate (LDR)** and **high dose rate (HDR)** fashion. With the former technique, multiple sources of low strength are placed in each catheter and remain for 3-5 days. During that time the patient is in the hospital with appropriate radiation exposure precautions for visitors and staff. With the high dose rate technique, a remote afterloader is employed to move a single source of high radioactivity to the assigned positions within the catheters. This takes place over approximately 10 minutes for each treatment fraction. Between treatments the sources are removed from the patient and there are no radioactivity precautions. Most patients have tolerated the multi-catheter technique well with minimal analgesic requirements, despite the common appearance of tissue edema during treatment. While this is the most challenging form of brachytherapy based APBI due to required precision in catheter spacing, it also offers the most conformality. As a result, the multi-catheter technique has few restrictions on size, shape, in-breast position, or proximity to sensitive structures such as the skin or nipple areolar complex.

A more recent development designed to simplify the placement and treatment design of brachytherapy based APBI is the balloon tipped catheter. The first such device and as yet the only one with FDA approval is the MammoSite Radiation Therapy System (RTS; Proxima Therapeutics Inc, Alpharetta, Georgia). This consists of a double lumen catheter placed transcutaneously either at the time of lumpectomy or post-operatively. (Figure 3) The balloon tip is inflated with saline to fill the lumpectomy cavity and move the surrounding tissue equidistantly from the center of the balloon for uniform dosing. Using the HDR technique, single or multiple dwell positions are employed for spherical or ovoid dose shells, respectively. The manufacturer makes two spherical balloon sizes: 5cm and 6cm diameters correspond to maximum fill volumes of 70cc and 120cc, respectively. An ovoid shaped balloon has recently been introduced and is being made available for clinical use. Post-placement imaging ensures uniform filling of the balloon, a high conformality with the lumpectomy cavity, and an adequate distance from the skin (minimum of 5mm). A treatment plan is designed to deliver the prescribed dose to a 1cm depth in tissue with twice daily treatment over 5 days. Since FDA approval in 2002, more than 4000 MammoSite balloons have been used. Follow-up data from the initial phase I/II data used for FDA approval have shown no undue toxicity at 21 and 29 months.[9,10] Additional long-term follow-up is ongoing to quantify long-term toxicity and efficacy.

While the two previously mentioned methods of brachytherapy deliver a fractionated course of radiation following surgery, methods in Europe allow for a single large dose of radiation to be given in the operating room following tumor removal. Single institution experiences include the use of either low energy (50 kVp) x-rays or electrons. In the former technique, a single dose is prescribed for either 5Gy at 1 cm depth or 20Gy at 0.2cm depth.[11,12] The latter technique uses surgical manipulation to assure the treatment volume is within range and normal tissue is adequately shielded; a single fraction of 21 Gy is applied.[13] The intraoperative technique offers minimal inconvenience to the patient and affords the normal tissue sparing and localization accuracy of other brachytherapy techniques. However, the timing of radiotherapy does not allow for evaluation of the surgical pathology to influence either the appropriateness of the patient for APBI or the prescription volume. In addition, the radiobiologic effect of a single large fraction vs. multiple smaller ones, both in terms of efficacy and toxicity, is the subject of ongoing investigation in this setting. At the time of this writing, both methods are being investigated in the phase III setting in Europe.

Brachytherapy has traditionally offered the best option for small volume tissue localization in a surgically approachable region, particularly when large fraction sizes can present unacceptable toxicity to adjacent structures. With the development of sophisticated computer planning and localization methods, 3-D CRT has been used successfully in APBI. (Figure 4) Advantages include a non-invasive approach and a more homogeneous dose distribution throughout the treatment volume. Methods have been published using multiple field design with the patient in

Table 1: Eligibility Criteria for APBI

	American Brachytherapy Society	American Society of Breast Surgeons
Age	≥45 years	≥50 years
Histology	Invasive ductal carcinoma	Invasive or in-situ ductal carcinoma
Size	≤3 cm	≤2cm
Nodal Status	Negative axillary lymph node dissection or sentinel lymph node procedure	Negative axillary lymph node dissection or sentinel lymph node procedure
Margin Status	No tumor at inked margin	No tumor within 2mm of inked margin

either the prone or supine position.[14,15,16] The primary disadvantage with this technique is the increased volume of normal tissue that receives low doses of radiation from the large number of fields. This is an inherent drawback for all conformal means of external beam radiotherapy, and the long-term effects are not well understood. This is especially relevant in the majority of potential APBI candidates who are otherwise healthy and have a long life expectancy. With further understanding of long-term effects of low dose radiation in this setting, more universal application of this method will be performed.

Toxicity profiles for APBI have been published, primarily from institutions using the interstitial multi-catheter technique. The most common toxicity involves the skin and subcutaneous tissue, as one might expect from the small treatment volumes and dose inhomogeneity inherent with brachytherapy. Data published from our institution using this technique have shown a high correlation between grade 3-4 subcutaneous toxicity (ie: fibrosis and fat necrosis) and the size of the volume treated.[17,18] In an experience reported by the Massachusetts General Hospital, dose escalation using an LDR technique resulted in a higher incidence of post-treatment biopsies, typically done for physical examination or mammographic findings consistent with fat necrosis on follow-up evaluation.[19] A toxicity analysis was recently published for the experience with the interstitial multi-catheter technique compared with the MammoSite RTS at both the Medical College of Virginia and at our institution.[20] Higher incidences of subcutaneous fibrosis (32% vs. 10.7%) and fat necrosis (12% vs. 7.1%) were seen with the multi-catheter method. This was exacerbated in those patients who received adriamycin based chemotherapy. This was also shown in a separate analysis of the multi-catheter LDR technique published by the Medical College of Virginia.[21] Due to the high doses per fraction with APBI, it is the generally accepted practice not to perform concurrent chemotherapy. Since the radiation is done within 2 weeks of surgery, chemotherapy is typically held until afterwards. To perform APBI following chemotherapy would require placement of a localization clip at the time of surgery, and would prohibit the use of the balloon-catheter, a method which requires an intact lumpectomy cavity.

Outcome data for APBI do not have the long-term follow-up enjoyed by traditional whole breast radiotherapy. The collective experience indicates an in-breast failure rate of approximately 5%, comparable to that of whole breast radiation. The majority of series report good-to-excellent cosmetic outcomes, contingent upon stringent patient selection criteria and meticulous treatment planning. Scrutiny of early experiences where in-breast recurrence rates were higher have revealed a lack of microscopic margin assessment, questionable target and dose volume delineation,[22,23] and dose prescription to the seroma cavity rather than the surrounding interstitial tissue at risk.[24] Long-term follow-up data with the MammoSite RTS are in the process of maturing. The oldest published data come from the phase I/II trial that led to FDA approval consisting of 43 patients. The ASBS has constructed a database of more than 1500 patients treated with the MammoSite RTS. Ongoing evaluation of this database will help determine the long-term efficacy and toxicity of the MammoSite RTS compared with other forms of APBI. Experiences in the United States with 3-D CRT used in APBI have resulted in excellent cosmetic outcome with as yet no published incidence of local recurrence. This technique uses variations on a multiple fixed beam beam design with specific patient immobilization. Although complex, this modality has generated a great deal of interest. The results of a phase I/II analysis (RTOG 03-19) examining the feasibility of this technique are forthcoming.[25] In Europe, several institutions have used external electron beam therapy for APBI. Higher than expected local recurrence rates again have been attributed to the lack of microscopic margin assessment and accurate dose volume delineation.[26]

Worldwide, several prospective randomized trials are investigating the use of APBI. In the United States, the NSABP B39/ RTOG 0413 national protocol recently opened and is seeking enrollment of patients. The study hopes to accrue 3000 patients, and randomizes them to either whole breast external beam treatment or APBI following breast conserving surgery with microscopic margin assessment. Acceptable APBI modalities include interstitial multi-catheter brachytherapy, balloon-tipped catheter brachytherapy, or 3-D conformal external beam radiotherapy. Strict quality assurance has been designed so that microscopic assessment of disease as well as dose prescription and evaluation will be accurate. At this time, not enough mature data exist to recommend APBI as a standard-of-care alternative to whole breast radiotherapy. One can assume that interest for this accelerated modality will grow among both patients and practitioners. The results of the ongoing randomized trials will be anxiously awaited.

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Radiation Management of Prostate Cancer

Arvin S. Glicksman, MD

Prostate cancer is the most frequent cancer in men, but not the most frequent cause of death. Most men die *with* prostate cancer, not *of* it. There has been controversy concerning the value of population screening for prostate cancer. The US Prevention Task Force recommends that men be *advised* concerning prostate cancer screening but does not *recommend* screening. Nonetheless, more men have prostate cancer screening than colorectal cancer screening.[1] With this intense screening activity over the last two decades, we have seen a decrease in the number of deaths from prostate cancer and a stage migration with the disease being diagnosed before widespread metastases brings the patient to the doctor.

With ubiquitous use of screening, controversy arises as to which men warrant biopsies. Some men with a PSA under 4 are harboring prostate cancer; the suggestion has been made that the rate of PSA change would be a worthwhile measure besides the PSA free in establishing a cancer diagnosis in these men.[2] Urologists still do not have firm guidelines for deciding which men under 50 (and over 50 as well) should have a biopsy.[3]

Having established the presence of prostate cancer, the question is: does this patient warrant treatment? If so, which treatment would be appropriate for him?. For instance, with low grade prostate cancers (i.e. Gleasons under 6 with PSAs under 10 in a man who has significant co-morbidities and estimated life expectancy of less than 10 years), no treatment (watchful waiting) may well be the most useful for him. With a more aggressive type of cancer (Gleason > 7, PSA > 10) in the same individual, treatment may be warranted since the disease may metastasize before the man would die of other causes.

Having decided a patient warrants treatment, there are a spectrum of treatments, all with advantages and disadvantages. Evidence indicates that surgical intervention or treatment by radiation are comparable in their outcome. In the past, before we could adequately stage the disease pre-operatively, surgery was "the gold standard." In the present era, when we can triage patients by age, PSA, Gleason score, and the presence or absence of extra-prostatic disease, there is little difference in outcome. Urologists usually select the most favorable cases, young men with organ confined disease, for surgical intervention. In the last decade, men have learned more about their treatment options, and many men are choosing non-surgical treatment. The choices include external beam radiation, brachytherapy, cryosurgery, and hormone therapy.[4]

"The outcome in terms of disease control is very much the same for surgery, external beam radiation or brachytherapy"

External beam radiotherapy has been an effective therapeutic intervention for over 30 years. A dose greater than 72 Gy has been found to most likely provide a curative outcome with 76 Gy having a more favorable outcome than 72 Gy. To achieve a dose of this magnitude, it is important to protect the normal surrounding tissue by performing conformal radiotherapy. In recent years, the addition of **IMRT (intensity modulated radiotherapy**) has made it possible to increase the dose even further without incurring unacceptable damage to the normal surrounding tissue. The addition of **IGRT (image guide radiotherapy)** allows the target volume in the prostate to be fixed within the beam of radiation throughout the course of treatment despite respiratory and other physiological movements that produce a 3 to 5 mm migration of the prostatic volume during irradiation. With these refinements, doses of 80 Gy are delivered without apparent increase in normal tissue toxicity.[5]

Patients with high risk disease, defined as Gleason 7 and above, and/or a PSA above 10, have been found to benefit from receiving their radiation in conjunction with total androgen blockade. In randomized clinical trials completed by the EORTC[6] and the RTOG[7], there was an approximate 15% improvement in disease free survival from the combined hormone plus radiation vs. radiation alone. Improved survival has been reported with continued adjuvant hormone therapy post radiation for 6 to 12 months. Prolonged hormone therapy brings with it its own problems; e.g., hot flashes, swelling of the breasts, weight gain as well as impotence. Long term androgen ablation increases the risk of osteoporosis and bone fractures and calcium replacement has been suggested,[8] but has not been proven effective. An increase of coronary artery disease may also occur.

Brachytherapy

In the mid 1970s, Dr. Basil Hilaris, a radiation oncologist at Memorial Hospital (now Memorial Sloan Kettering Cancer Center) with Dr. Willet Whitmore, the Director of Urology at Memorial, implanted radioactive gold seeds directly into the prostate by direct visualization. Although this technique showed that control of the cancer was possible, the morbidity associated with the procedure was unacceptable. Around 1990 with the introduction of ^{125}I and ^{103}Pd seeds using continuous ultrasound visualization guidance for the placement of the sources an acceptable alternative to external beam radiation or surgery has emerged. Brachytherapy, a team

effort by the radiation oncologist and the urologist, requires an hour or two of operating room time with a very short recovery. (Mayor Giuliani of New York was marching up Fifth Avenue in the Steubens Day Parade two days after his procedure.)

Each procedure, surgery, external beam radiation, or brachytherapy brings its own set of post-operative morbidity. Major concerns are incontinence, erectile dysfunction, dysuria, and rectal irritation.[9,10,11] Quality of life studies of men treated by these procedures has shown that there is no clear winner. Surgery may have more incontinence; brachytherapy, more rectal irritation, etc. The outcome in terms of disease control is very much the same for surgery, external beam radiation or brachytherapy. In a study commissioned by the American Brachytherapy Society, brachytherapy, external beam radiation, and surgery were compared for 5 and 10 year outcome. Data were collected in a uniform manner from five different institutions, categorizing patients according to age, presenting PSA, Gleason score.[5,6,7,8,9] The one caveat to remember is that brachytherapy has been performed for approximately 10 years in most institutions while external beam therapy has been a standard treatment for over 30 years as has been surgery for even longer. For the first 10 years at least, the data for each of these procedures are essentially the same. Whether brachytherapy will produce effective control at 20 years remains to be proven.

High dose brachytherapy (HDR) has been explored as an alternative to the standard ^{103}Pd or ^{125}I ultrasound guided permanent seed implant. In this procedure, ultrasound guided placement of catheters into the prostate is performed and are left in place. A precalculated placement of a high intensity iridium source into the catheters is done on three consecutive days, delivering a precalculated dose, which is biologically equivalent to that delivered by permanent seed implant. Although HDR equipment is available in Rhode Island, this procedure has not become a standard of care locally.

If primary treatment of the prostate fails, long term control by hormone manipulation has been well established in the urologic community. More recently protocols for chemotherapy combined with hormone therapy or chemotherapy alone are yielding worthwhile control rates and may in the future become a standard component of treatment both as a neoadjuvant as well as an adjuvant component of the entire process.

Prostate cancer remains an enigma for the oncology community. At what age should men initiate screening, if they should at all? Which men require treatment, if they require any at all? Which treatment should be chosen, if any treatment is to be given? We may not have the answers, but we certainly have advocates on all sides and increasing favorable outcomes and decreasing long term morbidity.

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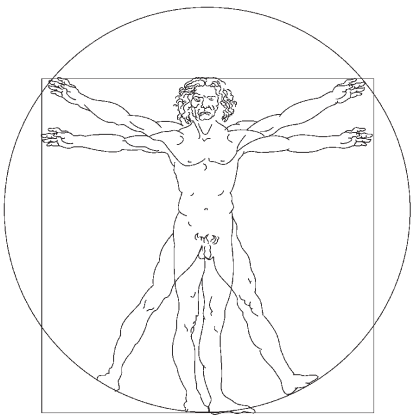

Intensity Modulated Radiation Therapy

Philip G. Maddock, MD, FRCR

The last twenty years have seen amazing improvements in the technical aspects of radiation oncology, resulting in devices such as the Gamma knife and more recently the Cyberknife, a small linear accelerator mounted on a robotic arm, that allow highly precise treatment of intracranial lesions and lesions of the spinal cord. By their very nature, however, indications for these devices are quite limited and most non-radiation oncologists will rarely come in contact with patients requiring such treatments.

For common cancers such as prostate cancer, breast cancer and head and neck cancers the major advances have taken place in three areas: 1) linear accelerator design, 2) oncologic imaging, and 3) computerized treatment planning systems. Combining all three of these advances has given us a technique to shape the dose distribution so as to increase the tumor dose while lowering the dose to adjacent radiosensitive tissues. This technique is called Intensity-Modulated Radiation Therapy or IMRT and is now the Standard of Care in radiation treatment for cancer of the prostate and cancers of the head and neck. With increased access to the Internet, many patients are well aware of IMRT. At least 20% of patients with prostate cancer presenting for their initial consultation at my office ask whether the facility has IMRT capability.[a] This paper describes the technical and clinical aspects of IMRT and how it benefits the patient with cancer.

Standard radiation therapy

Up to 1990 most radiation oncology centers had as a starting point a standard set of treatment plans for tumors in each anatomical location. Simulator films were taken and patient measurements were made. The information was fed into a treatment-planning computer; the resulting dose distribution was reviewed. Minor modifications in the dose distribution could be achieved by custom-designed shielding blocks cast for each individual patient or by changing the angulation for each portal.

Early cancer of the larynx was treated using standard right and left lateral portals to a dose of 66 cGy in 33 fractions and cure rates approached 90% at five years. There were minimal sequelae for normal tissues because the radiation portals for early cancer of the larynx are quite small and no radiosensitive structures were included. In contrast, similar but much larger right and left lateral portals were used to treat cancers of the base of tongue. Cure of tumors in this area however was associated with significant long-term side effects due to damage to the salivary glands, which were unavoidably irradiated to high doses. IMRT allows one to achieve a tumoricidal dose to the primary tumor while sparing the parotid glands and preserving salivary function.

"Is IMRT worth the added trouble and expense? The answer for cancers of the prostate and head and neck is a resounding yes."

IMRT

The main improvement in linear accelerator design has been the development of the multi-leaf collimator. (Figure 1) With monolithic collimators, modification of the dose distribution was achieved by using hand cast shielding blocks. Each block had to be inserted by hand which meant that treatment had to be interrupted after each portal so as to remove the first block and then insert the block for the second portal and so on. For a six-field 3D conformal plan for cancer of the prostate each treatment would take approximately thirty minutes, only five or six minutes of which was actual radiation exposure.

With a multi-leaf collimator the dose distribution in each field or portal can be continuously changed or modulated. A radical five-field IMRT plan for cancer of the prostate and approximately ten segments per field (an equivalent of approximately fifty separate fields) can be done in less than fifteen minutes.

The second advance to make IMRT feasible has been improved CT, MRI, and PET scans. A major improvement in the delineation of normal anatomical structures and in particular areas of nodal drainage has come from studies relating functional anatomy to diagnostic imaging studies.[b,c] The patient is seen initially in the radiation oncology department and scout films are taken on a simulator. Reference marks are tattooed and the patient is sent for a CT scan or MRI in the treatment position and with small alloy bb's on the reference marks. The imaging information is digitally returned to radiation oncology in a format that is readable by the treatment-planning computer. The surface contours are identified and, using the computer cursor or crosshair, the relevant normal anatomical structures are delineated. A patient, status post-surgery for a carcinoma of the left submandibular gland, is shown in Figure 2. Computer software allows one to depict the structures as a solid, transparent or wire frame figure. The tumor and other target volumes are also outlined.

The planning computer produces a list of all the structures and targets that have been entered from the CT data. The clinician or dosimetrist then enters into the treatment-planning document a set of dose parameters for each of these structures or targets. These parameters specify a minimum and a maximum dose for the tumor volume and different dose parameters might then be prescribed for each of the different organs or tissues that are to receive limited dose. Each of these dose parameters, or constraints, is then assigned a relative cost function, or weight. For radiosensitive normal structures a maximum radiation dose would be specified. For critical structures such as the spinal cord the maximum dose would be an absolute with a higher weight while for less critical structures it might be reasonable to specify that 95% or 85% of the volume of the structure should not exceed the tolerance dose (Table 1).

Given these parameters and contours, the treatment-planning computer will perform repeated iterations to generate a treatment plan that

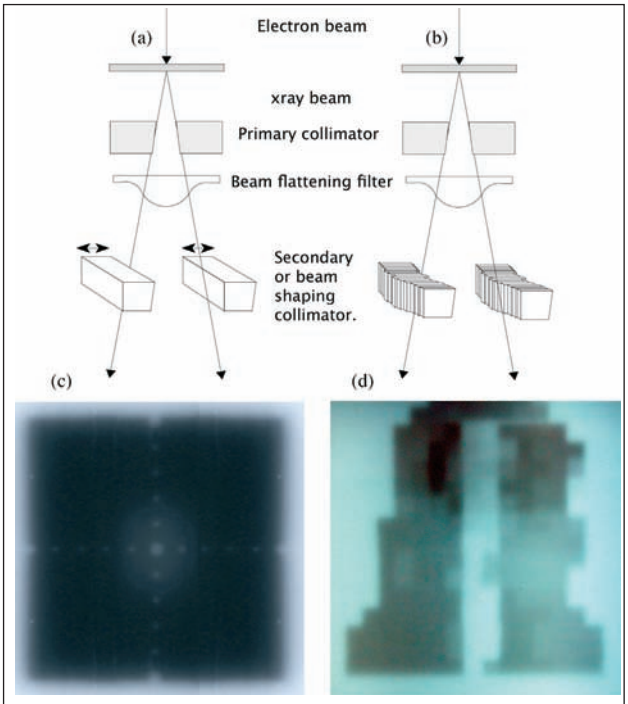

Figure 1
Linear Accelerator with (a) standard collimator on the left and, (b) a multi-leaf collimator (MLC) on the right. In (a), the beam is defined by a set of monolithic tungsten/lead collimators that give a square or oblong field of irradiation, as shown in the film on the left, (c). The beam can then be shaped by custom, molded lead shields unique to each field. In (b), the collimators are made of separate leaves, and each leaf is positioned by a servo motor. The servo motors are in turn controlled by a computer that is networked to the treatment planning system in the medical physics department. This allows the beam intensity to be modulated continuously during treatment, as shown in the cumulative dosimetry film on the right (d).

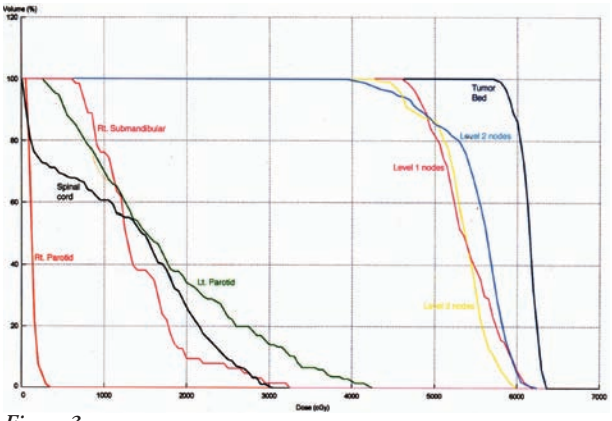

Figure 3
Dose Volume Histogram. In this particular IMRT plan, the right parotid sees virtually no radiation while only 40% by volume of the left parotid sees more than 2000 cGy. The spinal cord dose is similarly limited. 90% of the tumor bed volume receives more than 6000 cGy.

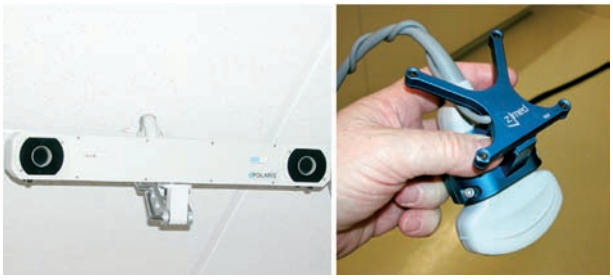

Figure 4
Image guidance using 3D ultrasound. The ceiling mounted stereoscopic digital cameras locate the ultrasound images by tracking the embedded reflectors in the handheld transducer.

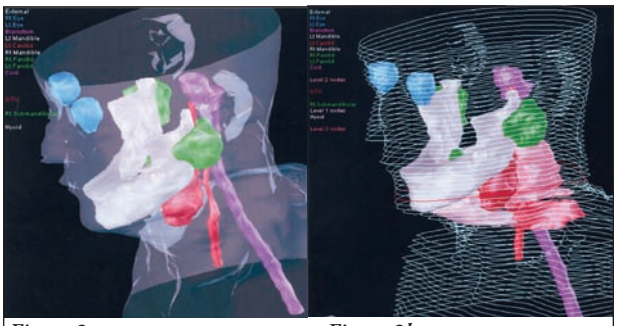

Figure 2a
The target volume has been added (red). The relevant normal structures are delineated. The spinal cord is purple, the parotids are green, and the mandible is white, etc.

Figure 2b
The level 1, 2, and 3 nodal groups have been added (deepening shades of pink).

best satisfies the entered constraints. This process takes from one to three hours of computation time. The optimized plan will specify the number and shape of MLC modulations of each portal, known as segments, and the discreet amount of radiation to be delivered through each segment to achieve the optimum dose distribution. The system will then generate a series of virtual X-rays to be compared with further stimulation films that are taken using the portal angles generated by the treatment planning computer. The 3D dose distribution is reviewed on the computer system and also on the dose volume histogram to see that all of the dose target and constraint parameters have been met. (Figure 3).

The final step in the implementation of an IMRT treatment course is to ensure accurate daily treatment setups throughout the full five to eight week course of treatment. Currently there are two systems for ensuring day-to-day accuracy of treatment. The first, which is usually limited to use in prostate cancer treatments, is to implant fiduciary markers in the prostate and to take a portal X-ray every day.[4,5] The main advantage to this system is its simplicity as the gold seeds are usually quite easily seen on the portal viewer. Relative disadvantages are that the gold seeds can occasionally migrate. Also, implanting the seed is an invasive procedure, done in patients who are already worn out by all the prior procedures.

An alternative method of daily localization is to use interactive, real-time ultrasound. In this system a pair of a stereoscopic digital cameras, mounted in the ceiling of the treatment room, is calibrated each morning so that the ultrasound transducer is integrated with the linear accelerator. The trans abdominal transducer is used to locate the prostate bladder and rectum relative to the isocenter of the accelerator and the 3D ultrasound images are fused with the patient's CT images. (Figure 4). Changes in the three axes of table movement are given so as to bring the prostate to the correct posi-

ORGAN AT RISK	Goal Full Volume Min. Dose (cGy)	Full Volume Min. Dose (cGy)	Goal Max. Dose (cGy)	Volume in Violation @ Goal Max. Dose (%)	Goal Overdose Volume (%)	Dose @ Goal Overdose Volume (cGy)	Goal Limit Dose (cGy)	Volume in Violation @ Goal Limit Dose (%)	Limit Dose (cGy)
Rt. Parotid	250	71.52	2000	0	10	181.29	2500	0	322.02
Lt. Parotid	250	281.58	2000	0	60	1255.23	2500	22.96	4245.08
Cord	250	31.91	3000	0	5	2750.32	4000	0	3023.12
Lt. Mandible	100	190.82	5000	11.86	5	5697.78	6000	1.74	6086.42
Rt. Submand.	250	608.54	2000	0	10	1984.53	2500	6.35	3243.71
Rt. Mandible	500	84.92	5000	2.4	5	5457.12	6000	1.08	6162.22
Brainstem	N/A	117.48	N/A	N/A	N/A	N/A	N/A	N/A	646.18
External	N/A	0	N/A	N/A	N/A	N/A	N/A	N/A	6365.68
Rt. Eye	N/A	50.88	N/A	N/A	N/A	N/A	N/A	N/A	127.62
Hyoid	N/A	2381.65	N/A	N/A	N/A	N/A	N/A	N/A	6177.51
Lt. Eye	N/A	54.36	N/A	N/A	N/A	N/A	N/A	N/A	115.57
Lt. Carotid	N/A	246.25	N/A	N/A	N/A	N/A	N/A	N/A	5849.08

Table 1

Analysis of how well the treatment plan achieves the dose constraints.

TARGET	Goal Minimum Dose (cGy)	Minimum Dose (cGy)	Volume in Violation @ Goal Min Dose (%)	Goal Prescription Dose (%)	Volume in Violation @ Rx Dose (%)	Goal Underdose Volume (%)	Dose @ Goal Underdose Volume (cGy)	Goal Limit Dose (cGy)	Volume in Violation @ Goal Limit Dose (%)	Limit Dose (cGy)
GTV	5500	5732.17	0	6000	11.74	2	5845.06	6400	0	6365.68
Level 1 Nodes	4250	4604.76	0	4500	0	2	4697.85	6400	0	6173.03
Level 3 Nodes	4250	4281.74	0	4500	0.13	2	4496.92	6400	0	5955.19
Level 2 Nodes	4250	3913.15	2.31	4500	2.36	2	4238.01	6400	0	6202.99
Margin: GTV	4750	4900.74	0	5000	0	5	5367.57	6400	0	6365.68

Table 2

Dose targets for tumor and nodal areas.

tion for treatment. This system is non-invasive and is more versatile as it can be used in sites that are inaccessible to implantation of a fiduciary marker. Patients like the ultrasound system and find the fusing of the three images on the ultrasound screen to be quite reassuring. A disadvantage is the steep learning curve for staff.

Is IMRT worth the added trouble and expense? The answer for cancers of the prostate and head and neck is a resounding yes. IMRT has improved local control rates while at the same time decreasing radiation induced side effects on normal tissues.[f,g,h,i] IMRT is also useful in certain types of breast cancer, particularly those involving the left breast in patients who have received Adriamycin, which is potentially cardiotoxic. Retrospective studies show that radiation to the myocardium can have consequences ten to fifteen years after treatment. IMRT plans reduce the myocardial dose dramatically. Studies in the use of IMRT at other anatomic sites continue.

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Hospital Case Files

Case presentations of the Brown University Department of Medicine Miriam Hospital Morbidity and Mortality Conference

Case of methemoglobinemia

Mary Hohenhaus, MD

Chief Complaint: Bright red blood per rectum

History of Present Illness: This 73-year-old woman had a recent medical history significant for renal and bladder cancer, deep venous thrombosis of the right lower extremity, and anticoagulation therapy complicated by lower gastrointestinal bleeding. Colonoscopy during that admission showed internal hemorrhoids and diverticulosis, but a bleeding site was not identified. Five days after discharge to a nursing home, she again experienced bloody bowel movements and returned to the Miriam Hospital emergency department for evaluation.

Review of Symptoms: No chest pain, palpitations, abdominal pain or cramping, nausea, vomiting, or lightheadedness. Positive for generalized weakness and diarrhea the day of admission.

Prior Medical History: Long-standing hypertension, intermittent atrial fibrillation, and hypercholesterolemia. Renal cell carcinoma and transitional cell bladder cancer status post left nephrectomy, radical cystectomy, and ileal loop diversion 6 weeks prior to presentation, postoperative course complicated by pneumonia, urinary tract infection, and retroperitoneal bleed. Deep venous thrombosis 2 weeks prior to presentation, management complicated by lower gastrointestinal bleeding, status post inferior vena cava filter placement.

Medications: Diltiazem 30 mg tid, pantoprazole 40 mg qd, epoetin alfa 40,000 units weekly, iron 325 mg bid, cholestyramine. Warfarin discontinued approximately 10 days earlier.

Allergies: Celecoxib (rash)

Social History: Resided at nursing home. Denied alcohol, tobacco, and drug use.

Family History: Non-contributory

Physical Exam:

Temp = 38.3C BP = 146/52 HR = 113 RR = 18 $Sa0_2$ = 98% room air
General: Pale, ill-appearing elderly female.
HEENT: Pale conjunctivae, oral mucous membranes moist.
CVS: Irregularly irregular, tachycardic.
Lungs: Decreased breath sounds at the bases.
Abdomen: Positive bowel sounds, soft, nontender, nondistended, gross blood on rectal exam.
Extremities: No cyanosis, clubbing, or edema.
Skin: Warm, normal turgor.
Neuro: Alert and oriented. Nonfocal.

LABS:

CBC:
WBC count: 6,500 per mL
Hemoglobin: 10.3 g/dL
Hematocrit: 31.8%
Platelet count: 248 per mL
Mean corpuscular volume: 86.5 fL
RDW: 18%

Chem 7:
Sodium: 131 mmol/L
Potassium: 3.5 mmol/L
Chloride: 98 mmol/L
Bicarbonate: 23 mmol/L
BUN: 11 mg/dL
Creatinine: 1.1 mg/dL
Glucose: 105 mg/dL

Coagulation studies:
PT 15.7 sec
INR 1.6
PTT 29.5 sec

Hospital Course: The patient received 1 liter normal saline and diltiazem (a total of 20 mg intravenously and 30 mg orally) in the emergency department. Emergency department personnel made several attempts to place a nasogastric tube for gastric lavage, but were unsuccessful. During her evaluation, the patient was noted to desaturate to 80% on room air, with an increase in her respiratory rate to 34 breaths per minute. She was administered 50% oxygen by nonrebreather mask, with improvement in her oxygen saturation to 89%. Computed tomographic angiography was negative for pulmonary embolism.

The patient was admitted to the medicine service for further workup and management of gastrointestinal bleeding and hypoxia. She was alert, awake, and hemodynamically stable, but remained tachypneic and hypoxic despite high-flow oxygen. She continued to perseverate on the fact that she had been unable to swallow the nasogastric tube earlier in the evening "even with that banana spray" (topical benzocaine 20%). While obtaining a sample for arterial blood gas (ABG) analysis, the medical team noted that the blood was abnormally dark. The sample was sent for co-oximetry as well, which revealed a methemoglobin level of 15.2%. ABG showed a pH of 7.41, PCO_2 31 mmHg, PO_2 374 mmHg, and oxygen saturation of 99%.

The patient was treated with methylene blue, with rapid resolution of tachypnea and improvement of oxygen saturation to 97% on 2 liters nasal cannula.

Discussion:

1. What is the mechanism of methemoglobinemia?

The oxygen-carrying moiety of

hemoglobin normally contains ferrous iron (Fe^{2+}). Oxidative stresses continually convert a small portion (0.5% to 3%/day) to the ferric form (Fe^{3+}), or methemoglobin. The presence of ferric iron alters the conformation of hemoglobin, rendering it unable to release oxygen to tissues and shifting the oxygen dissociation curve to the left.

Cytochrome b5 reductase is the major mechanism counteracting the oxidation of ferrous iron, maintaining the methemoglobin level at less than 1%. However, oxidizing chemicals can increase production of methemoglobin up to 1000-fold, overwhelming normal regulatory mechanisms and creating a functional anemia. For example, a patient with a hemoglobin level of 10 g/dL with 50% methemoglobin has only 5 g/dL of functional hemoglobin.

2. What agents are associated with acquired methemoglobinemia?

Numerous medications and industrial chemicals are implicated in development of methemoglobinemia.

In health care settings, nitrates, topical anesthetics, and sulfonamides are commonly implicated. In a retrospective study at Johns Hopkins University, 138 cases of methemoglobinemia were identified over a 3-year period. Dapsone, used primarily for *Pneumocystis* pneumonia prophylaxis, accounted for 42% of cases. The most severe cases of methemoglobinemia (5 cases) were associated with topical benzocaine use, with a mean peak methemoglobin of 43.8%. As a result of this review, Johns Hopkins removed benzocaine spray from its formulary given concerns that the dose delivered could not be adequately controlled. The recommended application for 20% benzocaine spray is a single spray lasting less than 1 second; a 1-second application delivers approximately 200 mg of drug. Application in excess of this amount increases the risk of adverse reactions.

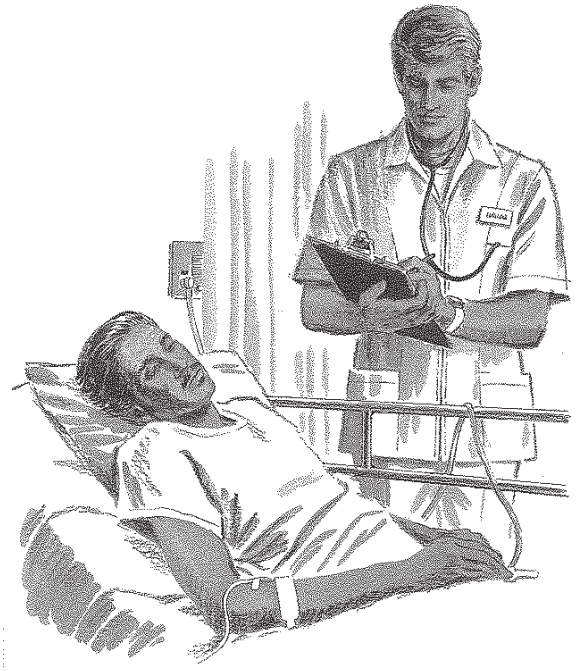
3. What is the presentation of acquired methemoglobinemia?

Healthy persons are rarely symptomatic until methemoglobin levels exceed 15%. Those with underlying anemia, cardiovascular disease, lung disease, sepsis, or hemoglobinopathies (such as sickle cell disease or G6PD deficiency) may be symptomatic at lower levels. Mental status change, headache, fatigue, exercise intolerance, dizziness, and syncope are associated with methemoglobin levels of 20% to 30%. Levels in excess of 50% are associated with arrhythmia, seizure, coma, and death.

Cyanosis typically becomes apparent at methemoglobin levels ≥1.5 g/dL. Blood appears dark or chocolate brown in color; exposure to oxygen does not cause a color change. Methemoglobin interferes with pulse oximetry, resulting in a "saturation gap", with pulse oximetry readings lower than calculated oxygen saturation by ABG analysis. Diagnosis is made by co-oximetry testing, which measures methemoglobin, carboxyhemoglobin, and oxyhemoglobin as a percentage of total hemoglobin.

4. What is the management of methemoglobinemia?

The offending agent should be discontinued. Supplemental oxygen alone may sufficient for mild symptoms. Treatment for patients with significant symptoms consists of 1% methylene blue (1 to 2 mg/kg IV over 5 minutes), followed by a saline flush. Methylene blue exploits a physiologically insignificant pathway for reduction of methemoglobin, serving as an electron donor for NADPH methemoglobin reductase. Methylene blue is contraindicated in glucose-6-phosphate dehydrogenase deficiency. Hemodialysis or exchange transfusion may be required in critically ill patients. Resolution of cyanosis is a poor marker for resolution of methemoglobinemia; serial co-oximetry tests should be monitored instead.



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STAGE AT DIAGNOSIS AND FIRST COURSE OF TREATMENT FOR PROSTATE CANCER IN RHODE ISLAND, 1990-2003

LEANNE C. CHIAVERINI, MPH, JOHN P. FULTON, PHD, AND JAY S. BUECHNER, PHD

Among Rhode Island males, prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer death.[1] The large majority of cases are diagnosed among men in their sixties and seventies. During the period 1987-2001, age-adjusted prostate cancer incidence increased by approximately 50% in Rhode Island, with most of the increase occurring in the early 1990s.[1] Over the same period, prostate cancer mortality decreased slightly, by approximately 8%, mostly in the late 1990s.[1]

Common screening tests for prostate cancer are the **prostate-specific antigen (PSA)** and the **digital rectal examination (DRE).** According to 2004 data from the Behavioral Risk Factor Surveillance System, 55% of Rhode Island men ages 40 and older had had a PSA test within the past two years and 68% had a DRE within the past two years.[2]

The most common treatment options for localized prostate cancer are radiation therapy (external-beam radiation therapy or implantation of radioisotopes), surgery (e.g., radical prostatectomy), a combination of therapies, or no immediate treatment, including "watchful waiting." These treatment options yield similar survival rates.[3] In addition to treatment efficacy, the patient's age, associated medical illness, and personal desires are considered when making treatment decisions.

This report presents cancer registry data from 1990-2003 on the stage of disease at diagnosis for prostate tumors diagnosed among men in Rhode Island and, for tumors diagnosed at a localized stage, trends in first-course treatment, specifically for radiation therapy and surgery.

METHODS

Information on all cases of prostate cancer diagnosed in Rhode Island between January 1, 1990, and December 31, 2003, was extracted from the Rhode Island Cancer Registry (RICR), run by the Rhode Island Department of Health in collaboration with the Hospital Association of Rhode Island. Tumors were categorized by the patient's age at diagnosis (under 60, 60-69, and 70 and over), stage of disease at diagnosis (SEER Summary Stage: localized, regional, distant, and unknown), and first course of treatment (radiation, surgery, hormone therapy, chemotherapy, biological response modifiers [BRM/immunotherapy], combinations of these, and no initial treatment). All trends were analyzed as three-year moving averages (i.e., 1990-1992, 1991-1993, …, 2001-2003).

RESULTS

The majority of prostate cancers diagnosed in Rhode Island are localized tumors. This proportion has slowly increased since the early 1990s (from approximately 55% in 1990-1993 to approximately 63% in the early 2000s), while the proportion of tumors diagnosed at a distant stage has slowly decreased. The proportion of prostate tumors diagnosed at a regional stage changed little over the 1990-2003 time period. The proportion of tumors not staged, approximately 27%, also changed little over the period. (Figure 1)

Among prostate cancers diagnosed at a localized stage, the use of radiation alone as first-course of treatment peaked at 36% in the 1994-1996 period, then decreased to 17% in 2001-2003. Radiation and surgery combined was used as a first-course of treatment in less than 10% of cases; this number decreased slightly over 1990-2003. The use of radiation in any other combination of treatments peaked in 1998-2000, then declined. Of this group, hormone therapy was used in approximately 99% of cases. In the early 1990s, surgery alone was used to treat 32% of prostate tumors; this proportion increased to 45% by the early 2000s. The frequency of no treatment decreased dramatically until the 1997-1999 period, then increased slightly until 2003. (Figure 2)

In Rhode Island, the use of radiation in the first course of treatment for localized prostate cancer is highest among men over age 70 and lowest among men under age 60. Since the late 1990s, trends in the use of radiation in the first course of therapy has fallen across all age groups. Among men over 60 years of age, the use of radiation increased until the late 1990s before falling. (Figure 3) In contrast, use of any surgery in the first course of treatment for localized prostate cancer was highest among men under age 60 and lowest among men age 70 and over. The use of surgery in the first course of treatment increased among men under age 70. (Figure 4)

CONCLUSION

In the 1990s and early 2000s, a majority of prostate cancer tumors diagnosed in Rhode Island were discovered as localized tumors. The increasing number of tumors diagnosed at a localized stage and the decreasing number diagnosed at a distant stage is a promising observation; this may be attributable to increased screening, to better screening techniques, or both. Screening may also be responsible for the increase in the incidence of prostate cancer diagnoses during the early 1990s.[1]

Over one-quarter of tumors were not staged, a proportion that remained relatively constant over the 1990-2003 period. Many prostate cancer cases cannot be staged at the time of diagnosis because many of the cases are not treated surgically. Surgery helps differentiate localized tumors from tumors that have spread regionally. Thus the tumors diagnosed among men ages 70 and over are more likely to be unstaged (38%) than tumors diagnosed among younger men (17%) because the former are much less likely than the latter to have surgery as part of the first course of treatment.

The proportion of localized pros-

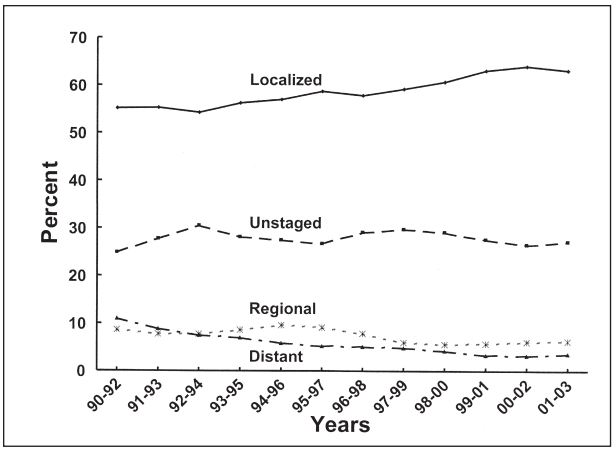

Figure 1. Prostate cancer stage at diagnosis, 3-year moving averages, RI, 1990-2003

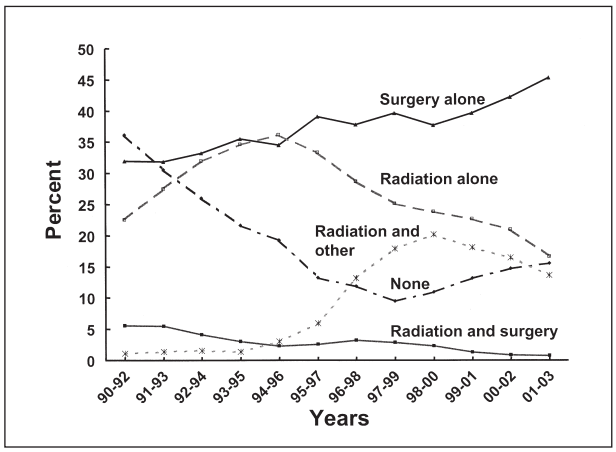

Figure 2. Type of initial treatment for localized prostate cancer cases, 3-year moving averages, RI, 1990-2003

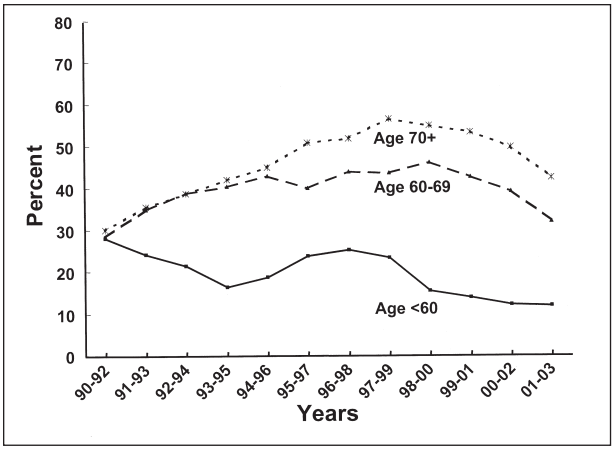

Figure 3. Use of any radiation as initial treatment for localized prostate cancer cases by age group, 3-year moving averages, RI, 1990-2003

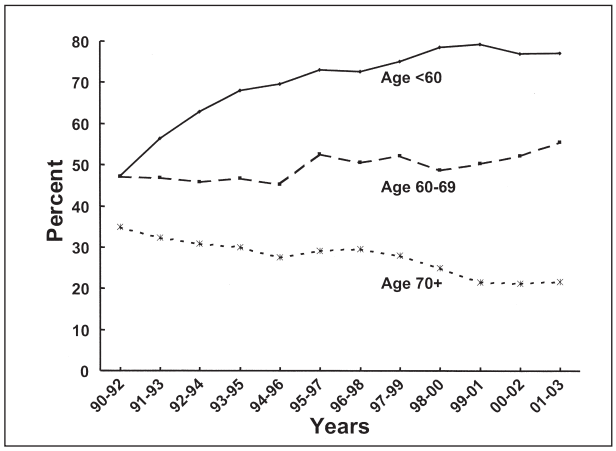

Figure 4. Use of any surgery as initial treatment for localized prostate cancer cases by age group, 3-year moving averages, RI, 1990-2003

tate cancer cases diagnosed in Rhode Island that received no initial therapy decreased dramatically from 1990 until 1997-1999, followed by a slight increase. National data from 1983-1995 demonstrate a similar trend with a decline that reached its lowest point in 1992.[4] Due to the nature of RICR treatment variables, the category of no treatment may or may not indicate "watchful waiting."

In Rhode Island, the use of radiation as part of the first course of treatment for prostate cancer peaked in 1998-2000, then decreased while the use of surgery increased. These trends are consistent with the SEER Program (National Cancer Institute), which show a shift towards more aggressive therapy, specifically radical prostatectomy.[4] In Rhode Island, treatment patterns vary by age, with a greater proportion of younger men receiving surgery and a greater proportion of older men receiving radiation therapy; this pattern is also observed in national data.[4] The shift towards surgery as a first course of treatment for localized prostate cancer may be attributable to improved surgical techniques, e.g., microsurgery, or to increased capacity for state-of-the-art surgery, or to a reassessment of the relative effectiveness of radiation versus modern surgical procedures. Although the impact of this treatment transition on mortality rates is unclear, it may have contributed to the recent decline in prostate cancer mortality rates observed locally and nationally.[1]

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Requirements for licensure of physicians in Rhode Island

State regulations state:

"Every physician licensed to practice allopathic or osteopathic medicine in Rhode Island under the provision of the Act and the regulations herein, shall on or before the first day of June of every even-numbered year after 2004, on a biennial basis, earn a minimum of forty (40) hours of AMA category 1/AOA category 1a continuing medical education credits and shall document this to the board.

"Said continuing medical education shall include a minimum of two (2) hours related to current information on any one or more of the following topics: universal precautions, infection control, modes of transmission, bioterrorism, OSHA, ethics, end-of-life education, palliative care, pain management, and other regulatory requirements."

Images in Medicine

A Case of Hypertrophic Nerve Roots

Michelle Mellion, MD, and James Gilchrist, MD

A 37 year-old woman with a long history of a slowly progressive, asymmetric, sensorimotor neuropathy thought to be either **Charcot Marie Tooth (CMT)** type 2 or **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)** had an MRI of the lumbar spine which showed multiple hypertrophic nerve roots. (Figure)

Hypertrophic nerve roots have been reported in CIDP and CMT type 1, both of which can also produce hypertrophic peripheral nerves.[1-3] Hypertrophy of nerves and nerve roots is not known to be associated with CMT type 2. Hypertrophic neuropathy can be seen in 11% of patients with CIDP.[3] This complication usually occurs after a long relapsing and remitting course and is thought to result from repeated bouts of remyelination. The incidence of nerve root hypertrophy is unknown in hereditary neuropathies.

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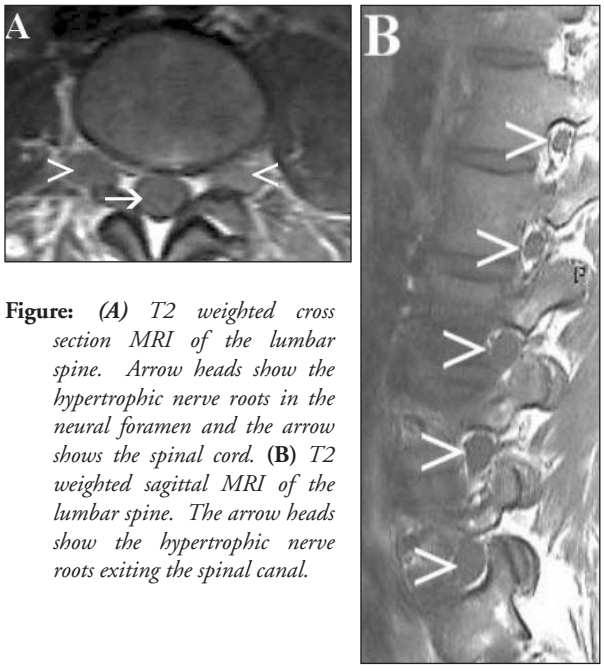


Figure: ***(A)*** *T2 weighted cross section MRI of the lumbar spine. Arrow heads show the hypertrophic nerve roots in the neural foramen and the arrow shows the spinal cord.* **(B)** *T2 weighted sagittal MRI of the lumbar spine. The arrow heads show the hypertrophic nerve roots exiting the spinal canal.*

Letters To The Editor

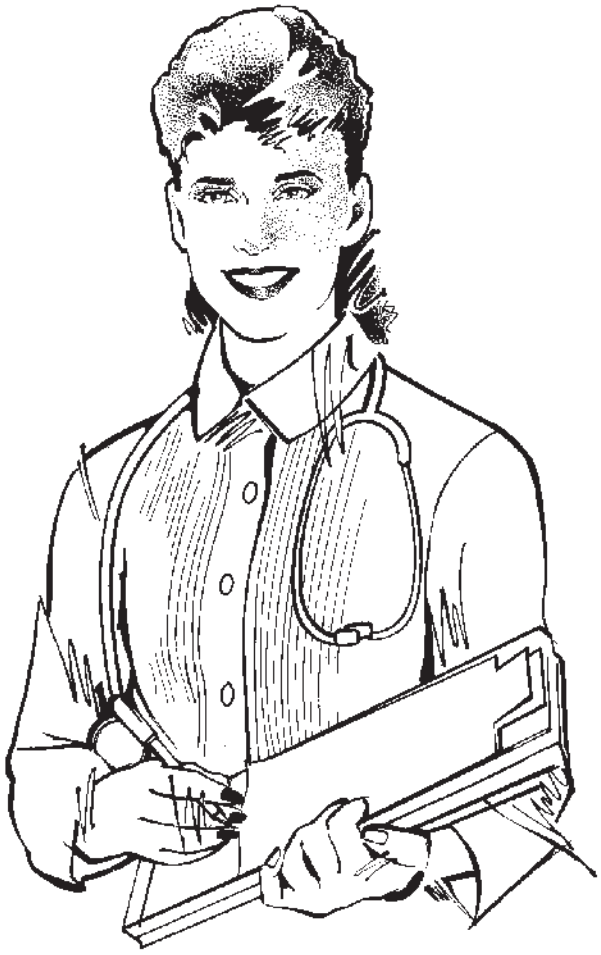
Editor,

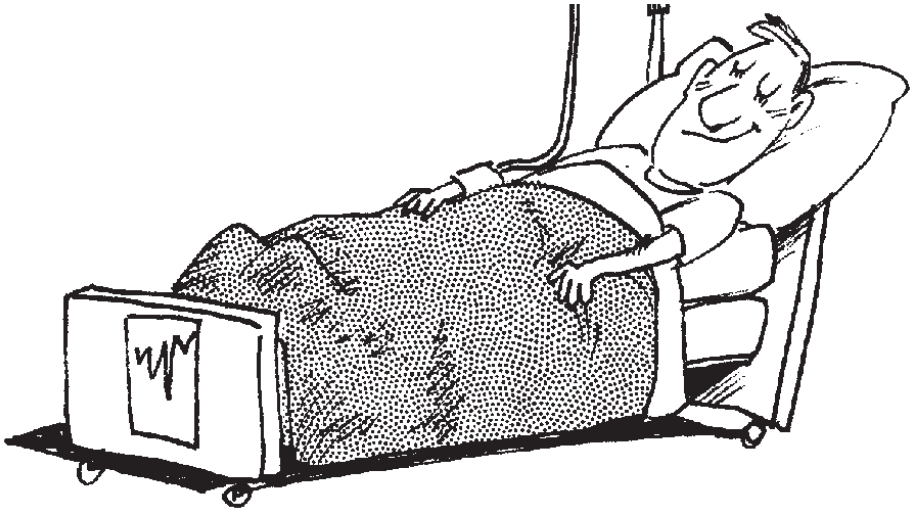
[Re Commentary, "The Surgeon General: Why Not Have One?" November 2005] I *have* heard Dr. Richard Carmona speak – right here in Rhode Island! I can assure you he really does "get it" in terms of the social and political determinants of the public's health. I also have had the privilege of hearing Dr. David Satcher speak on several occasions and meeting with him informally.

I suspect it would be impossible for any Surgeon General to make much positive progress on social issues with the current administration.

Should one quit in protest or stay and try to do the best one can? That is a deeply personal decision. Dr. Susan Wood, formerly of the FDA, made a different choice. She will certainly be replaced by someone more favorable to the administration's view.

Sincerely,
Donya A. Powers, MD
East Providence, RI





A Physician's Lexicon

Family Medicine in Words

Stanley M. Aronson, MD

The middle decades of the 20th Century witnessed the general practice of medicine transformed into the more formally structured discipline of family medicine with its own accredited residency training programs, a separate Board certification and independent clinical departments in most of the American schools of medicine.

The core concept of this newer clinical specialty resides in the word, family, derived from the Latin, *familia*, which in turn stems from an older Latin term, *famul*, meaning servant. A derivative word is *famulus*, meaning an attendant or one belonging to a household. The word, familiar, meaning commonly or generally known, or, occasionally, a member of the household, comes from the Latin, *familiaris*, meaning domestic, or pertaining to the home. And *paterfamilias* is a Latin term for the male head of the household.

Another English word pertaining to home and family is domestic, derived from the Latin, *domesticus*, which is, in turn, derived from the older Latin, *domus*, meaning house [or dome of the house]; and thus *domus Dei* means house of God, and *duomo*, a cathedral. To domesticate, to accustom one to household life, comes from the Latin, *domesticatus*, meaning to tame.

The Latin, *domus* is the precursor for a large number of English words such as indomitable [that which cannot be tamed]; domicile, from the Latin, *domicilium*, meaning household; domain, from the Latin, *dominium*, meaning property or estate; Dominican, the name of the religious order founded by St. Domingo de Guzman; dominie, meaning household master [but in Scotland meaning master of a school]; domino, meaning a robe worn by the head of the household - or a household game; and even belladonna, pertaining to the effects of atropine in dilating the ocular pupils and thus making women more alluring [derived from the Italian, *bella*, meaning beautiful and *domina*, the female head of the household.]

The word general, as in general practice, is from the Latin, *generalis*, meaning related to all. The derivative words in English include: genus, generic, genesis, genetic, genital, genealogy, degenerate, genial, gentile, homogeneous, gentry and genocide.

Rhode Island Department of Health
David Gifford, MD, MPH,
Director of Health

Vital Statistics

Edited by Roberta A. Chevoya, State Registrar

Rhode Island Monthly Vital Statistics Report

Provisional Occurrence Data from the Division of Vital Records

Underlying Cause of Death	Reporting Period			
	February 2005	12 Months Ending with February 2005		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	299	3,007	281.1	4,603.0
Malignant Neoplasms	190	2,484	232.2	6,597.0
Cerebrovascular Diseases	52	492	46.0	862.5
Injuries (Accident/Suicide/Homicide)	29	427	39.9	6,781.0
COPD	70	506	47.3	507.5

Vital Events	Reporting Period		
	August 2005	12 Months Ending with August 2005	
	Number	Number	Rates
Live Births	1108	13,228	12.4*
Deaths	746	10,219	9.6*
Infant Deaths	(7)	(93)	7.0#
Neonatal deaths	(4)	(77)	5.8#
Marriages	912	7,723	7.2*
Divorces	249	3,256	3.0*
Induced Terminations	386	5,316	401.9#
Spontaneous Fetal Deaths	96	1,034	78.2#
Under 20 weeks gestation	(91)	(958)	72.4#
20+ weeks gestation	(5)	(76)	5.7#

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,069,725

(c) Years of Potential Life Lost (YPLL)

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

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

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February 1916, Ninety Years Ago

An Editorial, "The Hospital and the Community," urged "…greater financial support…for privately endowed and supported hospitals which treat the worthy poor." It questioned the wisdom of "pay clinics," like the one at the Massachusetts General Hospital." where "the … patient earning a moderate wage may receive the best medical advice and treatment without feeling that he is an object of charity. It has long been recognized that the very rich and the very poor were two classes of our cosmopolitan population who could receive the best medical treatment – the rich because they were able to pay for it; the poor because it was free for the asking. The great middle class of hard-working, self-respecting citizens is oftentimes in danger of being deprived of the best medical advice because of inability to pay." The Editor was not convinced that pay clinics were "the best solution."

Ralph A. Goodwin, MD, in "Addison's disease, with the Report of 2 Cases," conceded: "On account of the many unsettled points as to the etiology and pathology of Addison's Disease, a scientific method of treatment is almost impossible." He discussed two cases: a 16 year-old boy who died two days after admission (diagnosis: tuberculosis of the adrenals), and a 25 year-old man who died four days after admission.

Ralph Emerson Taylor, MD, in "Renal Calculus: A Report of 7 Cases," noted that Hippocrates had mentioned kidney stones. He advised surgery as the treatment. He mentioned instances of misdiagnosis, mistreatment. One patient was misdiagnosed with addendicitis; another patient needed a nephrotomy instead of a pyelotomy because "the cortex was accidentally cut."

February 1965, Fifty Years Ago

The America Meat Institute took out a page-size ad, proclaiming the advantages of "Pork in the Human Dietary." The average intake was 46 pounds of lean pork and 20 pounds of bacon, per person per year.

Philip J. Lappin, MD, in "Congenital Hemolytic Anemia Associated with Spherocytosis," reported on the cases of a father and 3 of his children.

Francis H. Chafee, MD, delivered the Presidential Address: "Purpose of the Providence Medical Association." He cited the original Constitution, adopted Valentine's Day 1848: "…by … full interchange of views a harmonious unity of purpose may be achieved."

February, 1981, Twenty-Five Years Ago

An Editorial, "Caffeine: How Serious a Health Menace?" cited the FDA Commissioner's September warning to pregnant women to avoid, or use sparingly, caffeine-containing products. The Editorial, noting that warnings on nicotine and saccharin had not swayed the public's use, urged physicians to convey all three warnings to patients.

Cyrus Nemati, MD, and J. Gary Abuelo, MD, in "Cephalosporin-Induced Hypersensitivity Nephritis: Report of a Case Caused by Cefazolin," cautioned: "Prudence dictates avoidance of cephalosporins in penicillin-sensitive individuals."

William E. Boden, MD; Edward W. Bough, MD; Ian D. Benham; MD; and Richard B. Shulman, MD, contributed "The Coronary Care Concept: A Review of Past Achievements and A Glance Toward the Next Decade." They authors predicted "step-down or telemetry units would increase the cost-effectiveness of coronary care in hospitals."

What's in a Name???

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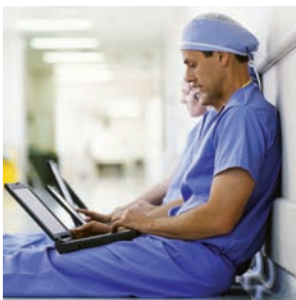

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