



The Role of Radiation Therapy in the Management of Lung, Prostate and Colorectal Cancer in South Dakota

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Abstract:

Radiation therapy has a pivotal role in the management of lung, breast, prostate and colorectal cancer. It is frequently used with curative intent as a single treatment modality or, more frequently, combined with chemotherapy and/or surgery. Radiotherapy also provides effective palliation of symptoms caused by locally advanced or metastatic disease. In this article, we review the role of radiation in the treatment of lung, colon and prostate cancer. We also discuss ongoing clinical trials and a unique cancer disparity program, “Walking Forward”, that investigates methods of improving access to cancer care, with the ultimate goal of improving cancer cure rates.

Introduction

Radiation therapy involves the use of ionizing radiation to eliminate or control the growth of malignant cells. Approximately 70 percent of cancer patients are treated with this modality during their disease course, whether for curative or palliative intent. Radiation is most commonly delivered using external beams of ionizing radiation generated by a linear accelerator. The shape, intensity, direction

and orientation of these beams can be modulated in order to deliver highly precise and conformal radiation doses to targets of all sizes anywhere in the body. Brachytherapy is one of the oldest forms of radiation and involves placing radioactive isotopes within the body, often directly in the tumor. The isotope emits gamma rays that transmit very high doses of radiation to the tumor and very little to the surrounding normal tissues. With either form of radiation,

the goal is to deliver tumoricidal doses with relative sparing of the adjacent tissues. The use of one form of radiation over the other depends upon the clinical scenario with the goal of achieving the optimal therapeutic ratio.

Radiation therapy plays a critical role in the management of the four most common malignancies affecting cancer patients in South Dakota. Radiation therapy can be curative when used either alone or in combination with other treatment modalities, such as surgery or chemotherapy in the initial management of lung, breast, prostate and colorectal cancers. For early stages of laryngeal and prostate cancer, radiotherapy alone yields high cure rates. For advanced stages of lung and rectal cancer (non-metastatic), radiation is combined with chemotherapy and/or surgery with curative intent. Radiotherapy also provides very effective palliation for locally advanced and metastatic cancers. The precise treatment strategy and its intent depend on the overall health of the patient, and on the tumor site, stage and location. In this article we will review the role of radiation in the management of each of the four most common cancers in South Dakota and will discuss some of the unique challenges these treatments may pose to patients living in our state.

Colorectal Cancer

Surgical resection and staging is critical in the potentially curative management of colorectal cancer. These malignancies are associated with a high risk for regional and microscopic spread. The risks of spread beyond the tumor depend upon the stage, tumor size and location. For colon cancer patients, there is a significant risk for occult liver disease. Adjuvant chemotherapy is administered in order to reduce the risk of relapse at distant sites, including the liver. Chemotherapy improves survival for these patients as demonstrated in numerous randomized trials.¹³ Chemotherapy is recommended for Stage 3 and 4 as well as some Stage 2 colon cancer patients.

Tumors arising in the rectum have a unique recurrence pattern among colorectal cancers and represent the largest subgroup of these tumors requiring adjuvant radiation therapy. In contrast to tumors arising in the colon, which predominantly recur at distant sites, the failure pattern associated with rectal cancers is characterized by a significant risk of local and nodal recurrence within the pelvis.⁴⁵ Once this pattern of failure was recognized, numerous trials incorporated radiation with surgery to reduce the risk of regional disease recurrence.

Early trials evaluated the use of radiation alone after surgery.

Patients with Stage 2-3 disease have the highest risk of locoregional recurrence after surgery. Numerous trials have demonstrated decreased rates of local or regional disease recurrence in such patients receiving adjuvant radiation therapy.^{6,7} Radiation alone, however, has not been associated with improved overall survival after surgery.⁸ This observation led to the incorporation of chemotherapy with radiation therapy in the adjuvant setting. Chemotherapy works as a radiosensitizer in the pelvis and also addresses micrometastases above the pelvis. Randomized trials have demonstrated both improved locoregional disease control and survival with the use of adjuvant chemoradiation therapy for Stage 2-3 rectal cancer.^{9,10}

There is now evidence that chemoradiotherapy before surgery (neoadjuvant) is more effective for certain patient subsets, compared to treatment after surgery (adjuvant).¹¹ Treatment before surgery can result in pathologic downstaging, improved local disease control and a higher probability of performing sphincter-preserving surgery.¹¹⁻¹³ Preoperative chemoradiation therapy was compared to postoperative chemoradiation therapy, with modern surgical techniques, in a landmark clinical trial that established preoperative therapy as the current standard treatment approach for patients with T3, T4 or node-positive rectal cancer.¹¹ This trial demonstrated improved local disease control, toxicity rates and sphincter preservation with preoperative chemotherapy and radiation therapy compared to postoperative treatment. All patients with rectal cancer should undergo careful preoperative staging, including transrectal ultrasound staging of the primary tumor, and should be referred to medical and radiation oncology before surgery to determine if they meet the above criteria.

Radiation therapy is also appropriate as adjuvant local treatment for patients with advanced colon cancers that extend into adjacent organs or structures, especially if the margins of resection are positive. Radiation can also be used to treat metastatic tumor deposits in a variety of anatomic locations. Stereotactic body radiation therapy is emerging as an effective treatment option for certain liver and lung metastases.^{14,15} Radiation also provides effective palliation for patients with advanced, symptomatic tumors arising in the colon or rectum.

Lung Cancer

Lung cancer is the most common cause of cancer death in the United States, with approximately 214,000 new cases diagnosed each year and 160,000 deaths.¹⁶ Eighty percent of lung cancers are classified as non-small cell lung cancer (NSCLC,) and 20 percent are small cell lung cancer

(SCLC). While both types of lung cancer are associated with exposure to tobacco smoke, they are managed quite differently due to different patterns of spread and biologic behavior. Radiation therapy plays an important role in the management of both major subtypes of lung cancer and is used for a number of disease presentations.

Non-small cell lung cancer is managed surgically when diagnosed early. Ideal surgical candidates are those with relatively small tumors confined to one lung without obvious mediastinal nodal extension (Stage 1 or 2 disease). Surgery for such patients yields high local control rates and is considered the treatment of choice when feasible.^{17,18} Patients must have adequate pulmonary reserve in order to undergo a successful surgical resection. Lobectomy is the preferred surgical approach and has been associated with improved local control, compared to less extensive surgery such as wedge resection or segmentectomy.¹⁹ Even after complete resection, rates of metastatic disease recurrence are significant. Therefore, adjuvant chemotherapy has been studied and has been shown to improve survival by five to 10 percent by reducing the risk of metastatic disease.²⁰ Patients with Stage 2 and higher disease experience the most benefit from adjuvant chemotherapy.

Patients with inadequate pulmonary reserve or severe medical comorbidities are considered poor surgical candidates, even when presenting with early stage disease. These patients can be treated effectively with definitive radiotherapy. Using conventional radiation treatment planning and dose fractionation, results are generally considered inferior to those potentially achieved with surgery.²¹ Radiation therapy, however, is still a curative treatment option for medically inoperable, early-stage lung cancer. The results achieved with primary radiation therapy correlate with the dose of radiation utilized and with the size and extent of the disease.

Over the last several years, stereotactic body radiation therapy (SBRT) has been developed as a more effective method to deliver radiation for medically inoperable early stage disease. Conventional radiation treatment for lung cancer requires six to seven weeks of daily treatments, each delivering a relatively low dose to the tumor. SBRT delivers a similar total dose of radiation, but compresses the treatment to between three and five very large fractions delivered over approximately two weeks. SBRT requires sophisticated equipment capable of ensuring accurate, precise delivery of the high dose radiation. South Dakota native Dr. Robert Timmerman has performed much of the pioneering work in developing SBRT as a viable treatment

option for medically inoperable NSCLC. Dr. Timmerman and others have published results from studies evaluating SBRT that compare favorably with results from surgical series, with local control approaching 90 percent at three years.²²⁻²⁴ Long-term experience with SBRT is developing, but this approach is rapidly becoming an important treatment option for patients with medically inoperable early stage disease, and has been incorporated in our own practice.

The management of Stage 3 disease requires a combination of treatment modalities and depends on the extent of disease and on the health of the patient. While chemotherapy and radiation are essential components of therapy for Stage 3 disease, patients without clinical mediastinal lymph node involvement may also undergo surgical resection. Surgery is appropriate for such patients who are healthy enough to undergo an extensive pulmonary resection. When surgery is performed as initial management of Stage 3 disease, it is followed by adjuvant chemotherapy. Radiation therapy is also considered after surgery for patients found to have positive surgical margins or mediastinal lymph node involvement, and has been associated with improved survival in several studies.^{25,26}

The combination of chemotherapy and radiation therapy followed by surgery (trimodality therapy) has also been studied in patients with Stage 3 disease with mediastinal lymph node involvement. The early results from the study of this treatment approach suggest improved progression-free survival with trimodality therapy compared with chemotherapy and radiation alone, but no improvement in overall survival.²⁷ The study demonstrated higher-than-expected rates of early mortality after surgery, especially for patients requiring a pneumonectomy. The risks associated with surgery in this study demonstrate the importance of a multidisciplinary approach in the management of patients with Stage 3 disease.

Chemoradiation therapy alone is the treatment of choice for patients with unresectable Stage 3 disease. Radiation plays a critical role in this combination of treatments, serving as the primary means of achieving local disease control. Radiation dose escalation has been associated with improved local disease control which, in turn improves overall survival.²⁸ Modern radiation treatment techniques allow for relatively higher, more effective radiation doses to be delivered with better sparing of the surrounding normal tissues. Definitive high-dose radiation therapy can now be delivered for primary lung cancer with reduced risk of treatment-related morbidity. A number of current studies

are evaluating the use of modern radiation techniques to increase dose beyond what is currently considered standard in order to continue to improve local control.

While radiation therapy alone can provide local disease control, metastatic failure is common. Chemotherapy combined with definitive radiation therapy can improve both local disease control and metastatic recurrence, thereby enhancing overall survival.^{29,30} The timing of combined chemotherapy and radiation therapy affects the outcome of treatment. Sequential chemotherapy and radiation therapy improves overall survival compared to radiation therapy alone.³¹ Concurrent administration of chemotherapy and radiation therapy aims to exploit the potential synergistic effect of chemotherapy when given with radiation. This approach has now become the standard of care and has been associated with better overall survival compared to sequential therapy for advanced disease.^{32,33}

Small cell lung cancer (SCLC) is managed quite differently and is distinguished from NSCLC by its rapid doubling time, high growth fraction and propensity to metastasize early in the course of the disease. Because of the biology and clinical behavior of SCLC, surgery has a limited role in its management. Chemotherapy and radiation will typically provide very high response rates, but recurrence is frequent both locally and at distant sites. Staging of SCLC is straightforward and relates to the feasibility of delivering definitive radiation treatment. Patients with disease confined to one side of the chest that can be safely treated with radiation therapy have limited stage disease. Those with tumors on both sides of the chest or with metastatic disease have extensive stage disease.

The mainstay of treatment for SCLC is chemotherapy because of its proclivity to metastasize early. Radiation therapy also plays a crucial role in the management of limited-stage disease. With chemotherapy treatment alone such patients experience very high rates of local disease progression. Numerous randomized studies and meta-analyses have suggested that thoracic radiotherapy, combined with chemotherapy, results not only in improved local disease control but also in improved overall survival.³⁴⁻³⁶ The timing of radiation therapy also appears important, as several analyses suggest that early initiation of thoracic radiation given with concurrent chemotherapy improves survival.^{37,38} Because of the rapid proliferation and high growth fraction of SCLC, accelerated radiation fractionation (shorter treatment duration) has been proposed as a potentially more effective treatment approach. One large study comparing twice-daily radiation treatments over

three weeks to once-daily radiation treatments over five weeks suggested an improvement in overall survival with the accelerated, twice-daily treatment approach.³⁹ The study has been criticized for the relatively low dose used in the once-daily arm but highlights the importance of aggressive radiation dosing for limited-stage SCLC.

Extensive stage disease is considered a systemic disease process and is treated primarily with chemotherapy. In spite of the widespread nature of extensive stage disease, response rates with chemotherapy are reasonable. Distant relapse remains a common occurrence, however. Patients with both limited- and extensive-stage disease develop brain metastases frequently, in part because of the limited penetration of chemotherapy within the brain. Reported rates of brain metastases are as high as 40 percent at one year, even after a complete or near complete response to treatment elsewhere in the body.^{40,41} Given the morbidity and mortality risks associated with brain metastases, prophylactic cranial irradiation (PCI) has been studied as a means to reduce their occurrence for patients with both limited and extensive stage disease. In separate studies, PCI has been shown to both reduce the risk of brain metastases and to improve overall survival in patients with either limited or extensive stage disease who respond to initial chemotherapy and/or chemoradiation therapy.^{40,41} PCI is now a standard consideration for those with both limited and extensive stage disease who respond to initial therapy. Radiation plays a key role in the management of SCLC and should be a part of the treatment strategy for patients with both limited and extensive stage disease.

In spite of the numerous advances in the management of both types of lung cancer, mortality rates remain high. Improved survival for both types of lung cancer will continue to occur only through continued basic and clinical research. It is, therefore, very important for oncologists to participate in clinical trials in order to improve the cure rates for these patients.

Prostate Cancer

Prostate cancer is the most commonly diagnosed non-cutaneous cancer, and is the second leading cause of cancer death among American men. Approximately 192,000 men were diagnosed with prostate cancer in the United States in 2009, and about 26,000 men died of the disease. American men have a one in six lifetime probability of developing prostate cancer.⁵⁸ Given the prevalence of prostate cancer, understanding the evaluation, risk stratification and potential treatment options associated with the disease is critical. In this section on prostate cancer, we review these issues

and discuss a number of potential treatment strategies. We also review ongoing clinical trials including those available in conjunction with our own community-based research program, which is sponsored by the National Cancer Institute (NCI).

Due to the widespread availability of serum prostate-specific antigen (PSA) screening, the incidence rates of prostate cancer have changed substantially over the last 20 years, rapidly increasing from 1988-1992 and leveling off since 1995. Approximately 50 to 60 percent of patients are now diagnosed with organ-confined disease. Risk stratification schemes using the clinical stage, PSA and Gleason scores (GS) are used to predict the likelihood of a patient having organ confined disease which guides therapy. The Gleason score, a measure of the aggressiveness of the cancer, is based upon the architectural pattern and is assigned a number between 4 and 10. The higher the number, the more aggressive the cancer. Risk stratification is also commonly used to predict biochemical and clinical outcome after treatment with either a radical prostatectomy (RP) or radiation.⁵⁹ The D'Amico stratification is most commonly used and describes favorable prostate cancer associated with PSA levels <10 ng/ml, Gleason score <7 and stage <T2A disease. Patients with favorable prostate cancer are considered to have a relatively low risk for extraprostatic disease, seminal vesicle involvement and pelvic lymph node metastasis with 10-year biochemical control rates as high as 80 to 90 percent with surgery or radiation. High-risk disease is characterized by >T2C disease, GS 8-10, or PSA >20; whereas, intermediate risk disease includes T2B, GS 7 and a PSA 10-20. Other emerging prognostic criteria include PSA velocity (PSA rise per year), percent positive cores and perineural invasion. Risk stratification is a critical first step in determining the optimal management of prostate cancer.

Active surveillance may be an appropriate option for low-risk patients who are agreeable to close follow-up and do not show any clinical or biochemical evidence of disease progression. It is also considered appropriate for elderly patients with significant medical comorbidities who have a relatively short life expectancy. Patients undergoing active surveillance should undergo regular PSA testing and should have biopsies of the prostate repeated at some point. Treatment should be considered if a repeat biopsy demonstrates a GS of 7 or above, or if the PSA doubling time is less than three years. For a more thorough discussion, please see reference No. 4.⁶⁰ There is now compelling evidence that definitive treatment for prostate cancer improves survival. A recent randomized Swedish study demonstrated that a radical prostatectomy (RP) improved survival by 5

percent over observation alone and was associated with a 50 percent reduction in prostate cancer mortality.⁶¹ While this study calls into question the appropriateness of active surveillance, a large randomized phase III trial is planned in the United States to randomize 2,100 men with prostate cancer to observation or definitive treatment. This study aims to determine whether some men with prostate cancer may safely avoid definitive treatment.

Excellent control rates are achieved for low-risk patients using single modality therapy. RP, permanent seed implant (PSI) or external beam radiotherapy (EBRT) are considered appropriate treatment options for low-risk disease.⁶² There have been no randomized trials comparing these three treatment options directly. The rates of disease control achieved with surgery or with definitive radiotherapy – whether a PSI or EBRT – are similar. There are no compelling data supporting the superiority of one treatment option over another. Selection of treatment is typically based on patient preference, convenience or potential short- or long-term toxicities, which differ with each treatment option.

For low-risk disease, external beam radiation will achieve high cure rates with minimal toxicities. The typical radiation doses delivered with contemporary techniques are significantly higher than they were several years ago. Radiation dose escalation has been associated with significant improvements in biochemical disease control (PSA stability) as demonstrated in four randomized trials.⁶³⁻⁶⁶ Prior to the last decade, it was not safe to treat prostate cancer patients above 70 Gy (35 treatments, Monday through Friday, at 2 Gy per day), due to high rates of bladder and rectal complications. With computerized treatment planning and increasingly complex radiation delivery systems, it is now possible to deliver 76 to 80 Gy with acceptable toxicities. Most radiation oncology centers use intensity modulated radiotherapy (IMRT) to dose escalate by using either a modified linear accelerator or a TomoTherapy unit. In 2004, the TomoTherapy program was implemented in Rapid City.⁶⁷ TomoTherapy delivers IMRT treatments through a process very similar to a CT scan.⁶⁸ The linear accelerator rotates around the patient while 64 multi-leaf collimators sculpt or “paint” the radiation dose. Radiation is passed through a binary collimating system, creating precise pencil-like beams of differing intensity to deliver radiation dose which conforms to the targeted area. External beam radiation is frequently used to treat prostate cancer since the acute toxicities are usually mild and well-controlled with medications, and there is long term clinical data supporting its safety and efficacy.⁶⁹ The disadvantages of EBRT include the inconvenience of daily treatments for

eight weeks and the cost.

The distance from the cancer center is often a burden and a barrier for patients to undergo cancer treatment, and in particular for low-risk prostate cancer patients considering EBRT. A phase II multi-institutional IMRT trial is open at our institution. In this study the number of treatments are decreased from 22 (2.94 Gy per fraction) to 16 (3.63 Gy) to 12 (4.3 Gy) by increasing the daily dose of radiation. These schedules were designed to give an equivalent dose of 76 Gy in 38 treatments. This trial has accrued 320 patients nationwide with 50 accrued in Rapid City. The current dose level is 3.63 Gy x 16 over four weeks. No significant toxicities have been encountered to date with excellent biochemical control rates at three years.^{70,71}

Permanent seed implant or brachytherapy is appropriate as monotherapy for low-risk patients with a prostate less than 50 to 60 grams, normal to near normal bladder function and no contraindications to general anesthesia. A transrectal, prostate ultrasound volume study is performed two to four weeks before the implant for radiation planning and to determine the anatomic feasibility of the procedure. The brachytherapy procedure is outpatient, takes 60 to 90 minutes, and is performed jointly by a radiation oncologist and a urologist. Radioactive iodine seeds are most commonly used and remain in the prostate permanently, but decay by six months to deliver an eventual dose of 145 Gy. The acute toxicities are higher compared to external beam radiation and include urinary irritative symptoms and changes in bowel habits. These usually resolve by four to six months. The Seattle Prostate Institute has performed 10,000 implants with 15 years of follow-up, demonstrating cure rates as high or higher than any other approach reported to date for low-risk disease.⁷² PSI is considered the most cost-effective treatment for low-risk disease and is more convenient. For patients who live a significant distance from a cancer center, this is often the most desired radiation treatment option. Technical expertise performing PSI is important, as improved biochemical control rates are clearly associated with the quality of seed implants.^{73,74} Thus, it is critical that patients who undergo permanent seed implants are treated at facilities that have adequate patient volume and expertise to maximize cure rates.⁵³

For patients with intermediate- and high-risk disease (non-metastatic), combination therapy is generally preferred. Surgery alone is often considered suboptimal for patients with a high risk of extraprostatic disease extension. Radiation in combination with androgen deprivation is the standard of care. Five randomized trials have demonstrated

the superiority of the combination approach compared to radiation alone.⁷⁵ An LHRH (luteinizing hormone-releasing hormone) agonist such as leuprolide or goserlin is most commonly used. On a molecular level it has been shown to promote apoptosis and may act synergistically with radiation-induced cell killing. There is emerging clinical data that a prolonged course of treatment may eradicate microscopic metastatic disease as well. The ideal length of androgen deprivation continues to be defined, but is often prescribed for six months in patients with intermediate-risk disease and for two to three years in high-risk disease.

Patients with intermediate- and high-risk disease may also be treated with IMRT combined with a brachytherapy boost. Several retrospective series have suggested higher and more durable biochemical control rates when patients undergo a PSI boost compared to EBRT alone.⁷⁶ Two phase II clinical trials are currently open for intermediate- and high-risk prostate cancer patients at our institution. For intermediate patients, treatment on study includes a short course of IMRT (2.2 Gy x 16), followed by a permanent seed implant boost (110 Gy). For eligible high-risk patients, the pelvic lymph nodes are treated on study to 56 Gy and the prostate to 70 Gy in 28 fractions with IMRT in order to decrease the overall treatment time from eight weeks to six weeks. The theme of these trials is to reduce the barrier of distance and time away from home, while maintaining or improving the therapeutic window.⁴⁸ In addition, higher daily doses of external beam radiation may enhance cell killing due to the radiobiology of prostate cancer cells.

The complications from radiation can be temporary or long term. The acute side effects are typically mild to moderate, transient and well controlled with medications. These include some degree of bowel, bladder and/or rectal irritation. The acute toxicities are enhanced when brachytherapy is the sole method of treatment or if used in combination with EBRT. With brachytherapy, there is a 20 to 30 percent risk of urinary retention requiring a Foley catheter for two to three days, in addition to the risk of bleeding, infection and anesthesia. More worrisome are the late or permanent complications that can take months or even years to develop. These include a 30 to 50 percent risk of erectile dysfunction (often reversed with medications) [all forms of radiation], 5 to 10 percent risk of a urethral stricture [brachytherapy], 1 to 5 percent risk of rectal bleeding [all forms of radiation], and <5 percent risk of bladder dysfunction, including a 1 percent risk of urinary incontinence [all forms of radiation]. Fistulas and bowel obstructions are rare with modern radiation delivery systems and techniques.^{69,76,77}

Currently, there are many effective treatment options for patients with prostate cancer. Although early detection is critical for successful treatment, even patients with more advanced stages of disease (non-metastatic) can be cured as described above. In order to improve cure rates, further characterization of the biology of prostate cancer, as well as participation in clinical trials will be essential.

“Walking Forward”, a Community-Based Research Program

“Walking Forward” is a community-based participatory research program in western South Dakota funded by the National Cancer Institute. The primary goal of this initiative is to address the high cancer mortality rates among American Indians by facilitating access to innovative clinical trials, behavioral and genetic research and tailored patient navigation (program detailed in a recent *South*

Dakota Medicine article by Kanekar and Petereit).^{48,56} The barrier of distance from the reservation to the cancer center has been partially addressed through patient navigation programs and participation in clinical trials for common disease sites such as prostate and breast cancer using brachytherapy and tomotherapy. These same studies also benefit the rest of the population in western South Dakota, as the entire region is considered medically underserved. (<http://bhpr.hrsa.gov/shortage/muaguide.htm>) “Walking Forward” was just funded for another five years by the NCI and will further focus on cancer prevention, education and screening, in addition to clinical trials and radiogenomics for both the American Indian and non-American Indian populations.

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