VOLUME 33 · NUMBER 9 · MARCH 20 2015

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

Brachytherapy: Where Has It Gone?

Daniel G. Petereit, *Rapid City Regional Cancer Center, Rapid City, SD*
Steven J. Frank, *University of Texas MD Anderson Cancer Center, Houston, TX*
Akila N. Viswanathan, *Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*
Beth Erickson, *Medical College of Wisconsin, Milwaukee, WI*
Patricia Eifel, *University of Texas MD Anderson Cancer Center, Houston, TX*
Paul L. Nguyen, *Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*
David E. Wazer, *Tufts Medical Center, Tufts University School of Medicine, Boston, MA, and Rhode Island Hospital, The Alpert Medical School of Brown University, Providence, RI*

I am generally a very practical person: that which works, works.
—Linus Torvalds

An article by Kavanagh et al[1] in a recent special issue of the *Journal of Clinical Oncology* highlighted several emerging technologies, translational frontiers, and novel clinical paradigms in radiation oncology. In the excitement generated by the plethora of these powerfully sophisticated tools now available to radiation oncologists, brachytherapy is often mistakenly viewed as an antiquated or even irrelevant modality, despite the central role it continues to play in the management of several cancer types. Further, having undergone its own remarkable recent technological advancement, brachytherapy continues to expand its potential application to a variety of clinical circumstances.

Brachytherapy is a specialized form of radiation therapy that entails the placement of an emitting radiation source (most commonly a radioactive isotope) in immediate proximity to macroscopic tumor and/or adjacent tissue at risk of harboring microscopic disease. Brachytherapy requires the positioning specialized applicators that are specifically designed for each anatomic site or clinical circumstance into body cavities and tissues. In many ways, brachytherapy can be considered the ultimate form of conformal radiation therapy because it is unparalleled in its ability to direct a large dose of radiation to the tumor while minimizing exposure to surrounding sensitive normal structures.

Brachytherapy has a long and storied history in the treatment of cancer. The first successful applications of radioisotopes to treat cancer were reported shortly after the discovery of radium in 1898. Over the next century and more, the evolution of brachytherapy into a valued component of the radiotherapy of many malignancies became firmly established. Notwithstanding this remarkable legacy of success, there is a disturbing trend in the United States whereby the use of brachytherapy is in rapid decline.[2-5] To briefly illustrate the profoundly negative consequences of decreasing the use of brachytherapy for cancer care expenditures, patient choice, treatment-related morbidity and, most alarmingly, cancer-specific mortality, two disease site examples are reviewed: prostate and uterine cervix.

PROSTATE CANCER

Approximately 70% of men diagnosed with prostate cancer present with low- or intermediate-risk disease.[6,7] Randomized trials assessing the relative value of therapeutic interventions have produced conflicting results.[8,9] Furthermore, there are reasons to suggest that many of these patients could be well-served by active surveillance. This has created uncertainty in the minds of both clinicians and patients leading most men diagnosed with prostate cancer in the United States to continue to receive local treatment of some sort. This trend is likely to persist until data are available from the first randomized trial comparing active surveillance to definitive treatment.[10] Among those men who choose to proceed with treatment, similar outcomes are achieved with prostatectomy, external beam radiation therapy (EBRT), or brachytherapy.[11] Although prostate brachytherapy is the least costly alternative, with outcomes as good as if not superior to other modalities, the use of prostate brachytherapy has seen a significant decline over the last decade.

Martin et al[2] used the National Cancer Data Base to study approximately 1.5 million patients who were treated between 1998 and 2010. They found that brachytherapy use reached a peak of 17% in 2002 and steadily declined to a low of 8% in 2010. Similarly, Mahmood et al[3] used the Surveillance, Epidemiology, and End Results (SEER) database to study approximately 182,000 patients treated between 2004 and 2009. They found that prostate brachytherapy procedures decreased from 44% in 2004 to 38% in 2009. Concurrently, the use of EBRT grew from 11.6% in 2004 to 24.0% in 2009. The most dramatic decline in brachytherapy procedures was seen at academic centers (48%), although it was also significant at comprehensive community (41%) and community cancer centers (30%).[2]

There are several reasons for the decline in prostate brachytherapy. First, there was an increase in the number of robotic prostatectomies. Surgery accounted for approximately 44% of treatments before the introduction of robotic prostatectomy in the early 2000s and then rose to 60% in 2010.[2] Second, there was an increase in the technical sophistication of EBRT, including intensity-modulated radiotherapy (IMRT), stereotactic radiotherapy (SBRT), and proton therapy. For prostate cancer, there has been a near-complete transition from the

use of conventional EBRT to IMRT over the past decade from 0.15% in 2000 to 95.9% in 2008. Third, reimbursement for IMRT is markedly higher compared with that for brachytherapy. This and other factors have led to the development of urologist-owned centers focused exclusively on delivering IMRT for prostate cancer.[12] The fourth reason is negative press, a result of cases of poor-quality prostate brachytherapy procedures leading to adverse clinical outcomes.[13] Fifth, the volume of prostate brachytherapy procedures used to train radiation oncology residents is suboptimal.[2] Compton et al[14] reported that the average number of interstitial prostate procedures decreased by 25% over a 5-year period when assessing the resident case load from the Accreditation Council of Graduate Medical Education resident case logs. And finally, for physicians with limited brachytherapy experience, the decision to offer brachytherapy may be negatively influenced by rigorous regulatory reporting requirements established by the Nuclear Regulatory Commission. For example, the Nuclear Regulatory Commission classifies even minor underdosing of some prostate tissue within an implant target volume as a reportable error.[15] As a consequence, brachytherapy may be perceived as being associated with excessive liability risk.

The decline of prostate brachytherapy with its comparable outcomes, low morbidity, and comparative cost-effectiveness poses immediate concerns related to patient choice, economic costs, and health policy. An analysis by Hayes et al[16] examined the cost of observation for a recently diagnosed prostate cancer as compared with initial treatment. The authors used a cost-effectiveness model that incorporated quality (or adverse effect) -adjusted life expectancy (QALE) with built-in assumptions that were favorably biased toward watchful waiting and active surveillance (AS). The analysis showed that for men age 65 years or older, AS was more effective (in terms of QALE) than all initial treatments (brachytherapy, surgery, or IMRT). Remarkably, brachytherapy was found to cost less than AS by $4,520 (based on a Medicare fee schedule). IMRT was similar to brachytherapy in QALE but was the most expensive, with an average lifetime cost of $48,699. Prostatectomy was associated with the poorest QALE and was also $2,806 more expensive than brachytherapy. Compared with all other options, brachytherapy was determined to be the most cost-effective initial treatment strategy.

Frank et al[17] performed a value analysis by using time-driven activity-based costing and outcome data for brachytherapy, IMRT, and proton therapy for intermediate-risk patients with prostate cancer. Brachytherapy was associated with the best value by using combinations of outcomes for the following domains: sexual function, urinary incontinence, urinary bother, bowel function, biochemical relapse-free survival, and cost. The authors concluded that "there is no greater value for the treatment of localized prostate cancer than brachytherapy."

For select patients with low- and intermediate-risk prostate cancer for whom definitive local treatment is deemed appropriate, numerous surgical and radiotherapeutic options exist. Current data would strongly suggest that prostate brachytherapy is the most cost-effective treatment approach for patients who have good-to-moderate bladder function as evidenced by lack of obstructive urinary symptoms. Unfortunately, current trends in use raise the unsettling prospect that prostate brachytherapy may soon be available in only a few select centers in the United States.

CERVICAL CANCER

The standard of care for the nonsurgical curative management of stage I to III cervical cancer includes a combination of chemotherapy, EBRT, and brachytherapy. Dose modeling studies unequivocally demonstrate that brachytherapy achieves the best radiation dose conformity, tumor dose escalation, and sparing of adjacent normal tissues when compared with advanced external beam modalities including IMRT and proton therapy.[18] Recent technological advances in image-guided planning and delivery of brachytherapy for cervical cancer report impressive local control rates of 100% for stage IB, 96% for stage IIB, and 86% for stage IIIB patients.[19,20]

Despite the excellent results achieved with brachytherapy for cervical cancer, a surprising number of patients do not receive it. Han et al[4] reported an analysis of 7,359 patients using the SEER database who received EBRT for cervical cancer between 1988 and 2009. During the period of the study, there was a 25% reduction in brachytherapy use and a 13% reduction in the cause-specific survival rate. Although a revision of the SEER coding manual may have partially accounted for a portion of the decline in the brachytherapy use and cancer-specific survival that was observed,[21] their study nonetheless raised concerns related to the potential for widespread practice of substandard care as a result of deviating from established treatment guidelines.

More recently, Gill et al[5] used the National Cancer Data Base to analyze the radiation dose-escalation technique that was used in the treatment of 7,654 patients with cervical cancer. From 2004 to 2011, use of brachytherapy decreased from 96.7% to 86.1% whereas use of IMRT and SBRT increased from 3.3% to 13.9% ($P < .01$). The median survival time was 70.9 months for patients who received brachytherapy compared with 47.1 months for those dose-escalated with either IMRT or SBRT as an alternative to brachytherapy. The risk of cervical cancer-specific death was significantly higher for women who did not receive brachytherapy (hazard ratio of 1.86) despite controlling for several relevant clinical and pathologic factors. Of particular note, the increase in the mortality rate was more pronounced for patients who did not receive brachytherapy than for those who did not receive chemotherapy.

The Quality Research in Radiation Oncology study reviewed the records of 261 randomly selected patients from 45 institutions who received radiation for cervical cancer from 2005 to 2007 and compared them to patients treated in the period from 1996 to 1999.[22] One of the key findings was that 13% of patients treated from 2005 to 2007 did not receive brachytherapy, almost double the rate that was observed in the earlier cohort.

Potential reasons for the reduction in the use of brachytherapy for cervical cancer include the preferential use of noninvasive radiation delivery systems such as IMRT and SBRT, financial incentives that provided motivation for using an alternative modality, inadequate training because of fewer brachytherapy cases for many radiation oncology residents, and inadequate maintenance of brachytherapy skills in both community and academic centers.[5]

It is estimated that the overall cure rate for cervical cancer in the United States could be improved by more than 10% if high-quality brachytherapy were to be performed for all appropriate patients. This is evident by compromised survival when brachytherapy is either

omitted or performed inadequately.[4,5,22] Without question, the inclusion of brachytherapy in the multimodality management of cervical cancer remains the standard of care for this disease.

In conclusion, patients with cancer deserve evidence-based care, including the delivery of high-quality, high-value brachytherapy. Continued education is essential to advance awareness of and expertise in the full spectrum of brachytherapy applications. The American Brachytherapy Society routinely offers semiannual schools for prostate, gynecologic (including cervical), and breast cancer so that radiation oncologists can maintain proficiency and competence in all contemporary brachytherapy techniques. In this era of increased public awareness of professional practice competency, the American Board of Radiology has implemented the Focused Practice Recognition in Brachytherapy as an element of its Maintenance of Certification Program. This recognition is achieved by participation in ongoing educational and practice quality improvement activities as well as special expertise in brachytherapy based on case volume reporting to a central data registry.

It is the responsibility of all oncologists to educate our patients, insurers, and policy makers about the critical value of brachytherapy. Brachytherapy not only works, it is an irreplaceable component of contemporary cancer care. It is time to bring brachytherapy back.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Kavanagh BD, Haffty BG, Tepper JE: Radiation oncology: A snapshot in time, 2014. J Clin Oncol 32:2825-2826, 2014

2. Martin JM, Handorf EA, Kutikov A, et al: The rise and fall of prostate brachytherapy: Use of brachytherapy for the treatment of localized prostate cancer in the National Cancer Data Base. Cancer 120:2114-2121, 2014

3. Mahmood U, Pugh T, Frank S, et al: Declining use of brachytherapy for the treatment of prostate cancer. Brachytherapy 13:157-162, 2014

4. Han K, Milosevic M, Fyles A, et al: Trends in the utilization of brachytherapy in cervical cancer in the United States. Int J Radiat Oncol Biol Phys 87:111-119, 2013

5. Gill BS, Lin JF, Krivak TC, et al: National Cancer Data Base analysis of radiation therapy consolidation modality for cervical cancer: The impact of new technological advancements. Int J Radiat Oncol Biol Phys 90:1083-1090, 2014

6. Andriole GL, Crawford ED, Grubb RL 3rd, et al: Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: Mortality results after 13 years of follow-up. J Natl Cancer Inst 104:125-132, 2012

7. D'Amico AV, Renshaw AA, Sussman B, et al: Pretreatment PSA velocity and risk of death from prostate cancer following external beam radiation therapy. JAMA 294:440-447, 2005

8. Wilt TJ, Brawer MK, Jones KM, et al: Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 367:203-213, 2012

9. Bill-Axelson A, Holmberg L, Ruutu M, et al: Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 352:1977-1984, 2005

10. Lane JA, Donovan JL, Davis M, et al: Active monitoring, radical prostatectomy, or radiotherapy for localised prostate cancer: Study design and diagnostic and baseline results of the ProtecT randomised phase 3 trial. Lancet Oncol 15:1109-1118, 2014

11. Grimm P, Billiet I, Bostwick D, et al: Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy: Results from the Prostate Cancer Results Study Group. BJU Int 109:22-29, 2012

12. Mitchell JM: Urologists' use of intensity-modulated radiation therapy for prostate cancer. N Engl J Med 369:1629-1637, 2013

13. Bogdanich W: Failed prostate procedures at the Philadelphia VA. New York Times, June 20, 2009

14. Compton JJ, Gaspar LE, Shrieve DC, et al: Resident-reported brachytherapy experience in ACGME-accredited radiation oncology training programs. Brachytherapy 12:622-627, 2013

15. Richardson S: A 2-year review of recent Nuclear Regulatory Commission events: What errors occur in the modern brachytherapy era? Pract Radiat Oncol 2:157-163, 2012

16. Hayes JH, Ollendorf DA, Pearson SD, et al: Observation versus initial treatment for men with localized, low-risk prostate cancer: A cost-effectiveness analysis. Ann Intern Med 158:853-860, 2013

17. Frank SJ, et al: Defining value in prostate brachytherapy. Presented at the University of Texas MD Anderson Cancer Center 2nd International Prostate Brachytherapy Conference: The Value and Future of Prostate Brachytherapy in a Changing Healthcare Environment, Houston, TX, December 7-8, 2013

18. Georg D, Kirisits C, Hillbrand M, et al: Image-guided radiotherapy for cervix cancer: High-tech external beam therapy versus high-tech brachytherapy. Int J Radiat Oncol Biol Phys 71:1272-1278, 2008

19. Pötter R, Georg P, Dimopoulos JC, et al: Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. Radiother Oncol 100:116-123, 2011

20. Lindegaard JC, Fokdal LU, Nielsen SK, et al: MRI-guided adaptive radiotherapy in locally advanced cervical cancer from a Nordic perspective. Acta Oncol 52:1510-1519, 2013

21. Smith GL, Eifel PJ: Trends in the utilization of brachytherapy in cervical cancer in the United States: In regard to Han et al. Int J Radiat Oncol Biol Phys 88:459-460, 2014

22. Eifel PJ, Ho A, Khalid N, et al: Patterns of radiation therapy practice for patients treated for intact cervical cancer in 2005 to 2007: A quality Research in Radiation Oncology study. Int J Radiat Oncol Biol Phys 89:249-256, 2014

DOI: 10.1200/JCO.2014.59.8128; published online ahead of print at www.jco.org on February 9, 2015

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Brachytherapy: Where Has It Gone?

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Daniel G. Petereit
No relationship to disclose

Steven J. Frank
Stock or Other Ownership: C4 Imaging
Honoraria: Varian Medical Systems, Elekta, Hitachi Chemical, IBA
Research Funding: Elekta
Patents, Royalties, Other Intellectual Property: C4 Imaging
Travel, Accommodations, Expenses: Elekta

Akila N. Viswanathan
Travel, Accommodations, Expenses: Elekta

Beth Erickson
No relationship to disclose

Patricia Eifel
Patents, Royalties, Other Intellectual Property: Adaptive Intracavitary Brachytherapy Applicator - Patent, The University of Texas MD Anderson Cancer Center and Nucletron

Paul L. Nguyen
Consulting or Advisory Role: Medivation, Abbott Laboratories (I), GenomeDx
Patents, Royalties, Other Intellectual Property: Wife has a patent on volatile diagnostics of infections (I)

David Wazer
Consulting or Advisory Role: Advanced Radiation Therapy
Patents, Royalties, Other Intellectual Property: Stapler source brachytherapy patent, Publication royalties; Wolters Kluwer, Publication royalties; UpToDate