

EDITORIAL

Curative Radiation Therapy for Locally Advanced Cervical Cancer: Brachytherapy Is NOT Optional

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The standard definitive treatment for locally advanced cervical cancer includes both external beam radiation therapy (EBRT) and brachytherapy. Brachytherapy is necessary to deliver a highly effective dose to the primary tumor: more than 80-85 Gy biologically equivalent dose in 2-Gy fractions (EQD2) can routinely be delivered to the tumor periphery while the central cervix receives even higher doses (>120 Gy EQD2). The ability to safely deliver a high dose to central disease undoubtedly explains the excellent local control rates that can be achieved when cervical cancers are treated with a combination of EBRT and brachytherapy.

Recently, Han et al (1) published Surveillance, Epidemiology, and End Results (SEER) data for brachytherapy use in patients treated for cervical cancer in the United States. In that study of 7359 patients who received EBRT between 1988 and 2009, only 63% were also reported to have received brachytherapy. Furthermore, the rate of brachytherapy use fell from 75%-80% in the 1980s and 1990s to <60% after 2003. Importantly, patients who were treated with combined EBRT and brachytherapy had a significantly better overall survival than those treated with EBRT alone (65% and 50%, respectively); there were no significant differences in non-cancer-related deaths between the 2 groups.

Repeating painful mistakes from the past

Brachytherapy has been an essential component in the successful treatment of cervical cancer for more than 100 years. When

25-MV photon beams became available in the 1970s, investigators seeking to exploit the new technology in stage IIIB patients explored the use of shrinking EBRT fields to deliver central doses of 60-70 Gy; brachytherapy was markedly reduced or even eliminated (2). This apparently logical approach resulted in significantly poorer survival rates (and higher complication rates) than treatments that emphasized brachytherapy. Although it took years to recognize the inferiority of this approach, it was eventually abandoned (2). Patterns of Care studies (PCS) from the 1970s also consistently demonstrated significantly worse outcomes when brachytherapy was not used (3). Despite this evidence, PCSs from the 1990s demonstrated a disturbing failure of cervical cancer treatments to meet guidelines for optimal treatment with an unacceptably high proportion of patients treated using EBRT only (4). This trend persists in the most recent PCS from 2005 to 2007, where nonacademic centers, in particular, failed to consistently use brachytherapy (5).

The data from Han et al (1) suggest that clinicians continue to ignore past experience, perhaps once again seduced by new EBRT technologies, such as intensity modulated radiation therapy (IMRT) and stereotactic body RT (SBRT), into believing that these techniques could replace brachytherapy in the treatment of cervical cancer. However, careful study of the relevant physics shows that brachytherapy can deliver significantly higher doses to the target while minimizing dose to the normal tissues than even the most conformal IMRT, SBRT, or proton techniques. It therefore comes as no surprise that the recent study by Han et al (1) demonstrated a poorer survival rate when brachytherapy was not applied.

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Reasons for decline in reporting of use of brachytherapy

Han et al (1) observed a decline in SEER reporting of the use of brachytherapy starting in 2002 that persisted throughout the duration of the study until 2008. The authors hypothesize that this decline could represent a move by some clinicians to replace brachytherapy with IMRT. In surveys of US radiation oncologists, the percentage of those using IMRT for gynecologic applications increased from 15% in 2002 to 27% in 2004 (6). However, those surveys did not indicate how IMRT was used. At the time, most reports used IMRT to spare normal tissues during whole-pelvis irradiation; it is likely that much of the increase in use of IMRT reflected this type of application.

Another factor that might have contributed to apparent low rates of the use of brachytherapy is the tendency for SEER to underreport radiation therapy use. PCSs from 1996 to 1999 (4) and 2005 to 2007 (5) indicate rates of brachytherapy use of approximately 90% during those periods, higher than the 70%-80% and 60% rates, respectively, reported by Han et al (1). Furthermore, a change that occurred in 2003 that greatly increased the complexity of SEER brachytherapy coding (7) could explain some of the decline reported by Han et al (1). However, although caution should be used in interpreting records from SEER, the data do suggest that there might have been a real decrease in the use of brachytherapy after the year 2000. Several explanations for such a decline may be considered and taken into account, such as inappropriate applications of EBRT, decreasing brachytherapy training and expertise, and failure of clinicians who lacked the ability or resources to administer brachytherapy to refer patients to centers with greater expertise.

Importance of training, expertise, and patient volume

Brachytherapy, like any complex medical procedure, requires training and expertise for optimal application. A recent paper on radiation oncology training programs from 2006 to 2011, reports that trainees treated an average of 45 intracavitary cases during the course of their training, according to experience obtained in Accreditation Council for Graduate Medical Education (ACGME) (8). Trainees treated an average of 45 intracavitary cases during the course of their training. Although this number may appear ample, many may be vaginal cuff treatments. Experience with these straightforward cases does not add meaningfully to clinicians' expertise in techniques required for cervical cancer brachytherapy. Furthermore, it is of concern that a large variation in experience was seen as 30% of residents reported treating less than 15 intracavitary cases during their training.

Perhaps more importantly, maintenance of brachytherapy skills undoubtedly requires a minimum level of continuous experience after training. In most practices, the number of new cases is insufficient to provide this experience. It has been estimated that 50% of facilities treat <3 cervical patients per year (4). With such a small volume, it is not possible to maintain routine procedures, and it is difficult to adequately accommodate new developments in the field. The adverse consequence of low patient numbers are clearly demonstrated by the fact that patients treated in small-volume centers are less likely to receive brachytherapy, tend to

receive a lower dose to point A, and require a longer average time to complete treatment (4). All these factors have been shown to influence patient outcome. Brachytherapy requires specific skills in a multidisciplinary team embracing radiology, radiation oncology, and medical physics. This expertise can be maintained only by seeing patients regularly. In our opinion, centers not treating a minimum of 10-15 cervix cancer patients per year should consider referring patients to a center with greater volume.

Prospects of improving outcome with image guided adaptive brachytherapy

Brachytherapy expertise and the ability to apply new brachytherapy technologies are essential if we are to advance the quality of cervical cancer radiation therapy. During the last decade, image guided adaptive brachytherapy (IGABT) was introduced as a means of tailoring treatment to tumor response and variations in individual anatomy. Poorly responding tumors with persistent gross disease after doses of 40-45 Gy are more likely to recur locally. IGABT provides an opportunity to improve outcome by increasing the dose to large, poorly responding tumors and to spare critical structures for patients whose tumors have responded well (9). Magnetic resonance imaging (MRI) provides the most detailed images for IGABT. Mono-institutional IGABT series of 156 and 140 patients from Medical University of Vienna and Aarhus University Hospital, respectively, have demonstrated excellent outcomes with 3-year actuarial local control rates of >90% (10, 11). Pötter et al (11) reported local control rates of 100% for stage IB, 96% for stage IIB, and 86% for stage IIIB cervical cancers. Compared with earlier patients treated without image guidance, patients treated with IGABT appeared to have higher overall survival rates and less major morbidity (10, 11). However, prospective multicenter studies are needed to provide sound clinical evidence of improved outcome to justify the added expense of this approach. In 2008, the Groupe Européen de Curiothérapie and the European Society for Radiotherapy and Oncology (GEC-ESTRO) gynecology network initiated the international study of MRI-based brachytherapy in cervical cancer (EMBRACE) (www.embracestudy.dk). EMBRACE has so far recruited more than 1000 patients from 30 international centers. Appropriate application of IGABT requires specific training in applicator insertion, target contouring, treatment planning, and optimization. Investigators report that a typical IGABT learning curve requires 10-15 patients treated within a reasonable time span.

Conclusions

Many studies, including that by Han et al (1, 2, 4), demonstrate the critical importance of brachytherapy in treatment of cervical cancer. The evidence that many US physicians fail to meet current guidelines and the suggestion that they may be attempting to replace brachytherapy with external beam boosts is worrisome. The limited experience in many centers treating cervical cancer is also a major concern. Taken as a whole, these data suggest that many women are receiving inadequate treatments that could result in unnecessary recurrences, toxicities, and even deaths. A new drug yielding a 10% survival improvement would be heralded as a great advance. Ironically, it is likely that we could achieve similar

improvements in the outcome of patients with cervical cancer by simply applying tried and true radiation therapy techniques using best practice guidelines. Eventually, further improvements through image guided brachytherapy techniques may be realized if we recognize the critical importance of high-quality brachytherapy in the delivery of effective radiation treatment for women with locally advanced cervical cancer.

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