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Review

Intensity modulated radiotherapy in gynecologic cancers: Hope, hype or hyperbole?

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HIGHLIGHTS

- IMRT's use in gynecologic cancer is evolving
- The use of IMRT in postoperative gynecologic cases should be considered
- Care must be taken with the use of IMRT secondary to unique planning concerns.

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ABSTRACT

Significant advances have occurred within the field of radiation oncology within the past few decades. Treatment with external beam radiotherapy has progressed from treatment fields planned from bony anatomy seen on planar X-rays, to 3-dimensional planning utilizing fused MRI's and PET images. Recently, intensity modulated radiotherapy (IMRT) has been integrated into many areas within radiation oncology, and its role in the treatment of gynecologic cancers is evolving. Potentials exist for improvements in both treatment toxicity, as well as improved efficacy through advances in treatment delivery. Unique challenges are also raised, however. With increased accuracy of treatment delivery comes the need for greater accuracy in target delineation and incorporation of motion to prevent marginal misses. The goal of this review is to evaluate the use of IMRT in cervical and endometrial cancers, including the results of dosimetric and clinical studies to date. In addition, potential disadvantages and challenges of IMRT integration are discussed.

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Introduction

The incidence, mortality and treatment of gynecologic cancers have changed dramatically over time. For example, cervical cancer previously was the most common cause for cancer death among women; however, with the advent of screening programs, cervical cancer has fallen to being the third most common gynecologic cancer in the US, and is not even on the list of the ten most common or lethal cancers in women [1]. Significant treatment advances have also occurred in the past several decades; refinements in operations have reduced morbidity and length of hospital stays, and multiagent chemotherapy has been integrated, dramatically improving survival in disease such as ovarian cancer [2], as well as impacting outcomes in other disease sites [3–10].

Within radiation therapy, three substantial developments have permitted rapid advancement: imaging, computer power, and MLC development [11]. Advances in imaging with wide availability of CT, MRI and PET and have permitted near uniform availability of three-dimensional treatment planning where volumetric coverage of targets is easily measured by dose volume histograms (DVHs). Importantly, organs at risk (OARs) can be delineated and, consequently in many cases, radiation to these organs can be avoided. Computer power has also advanced to the point where complex dose computations can be performed in minutes that previously would take days. In addition, while the basic design of the linear accelerator is largely unchanged, development of the multileaf collimators to shape fields and obviate clumsy and time-consuming blocks has paved the way for computer-controlled radiation delivery [11,12]. In gynecologic cancers specifically, external beam radiotherapy (EBRT) has evolved from traditional 4-field box designs, where pelvic fields were treated based off of bony anatomy landmarks on fluoroscopic films, to 3-D conformal therapy, where CT scans are performed and treatment apertures are conformed to the shapes of targets and normal tissues. Even more recently intensity modulated radiotherapy (IMRT) has been utilized, where the intensity, or fluence, of each beam is purposely altered by the summation of hundreds of beamlets in order to satisfy clinical goals of target and normal tissue doses. Simultaneously, improvements in both diagnostic imaging as well as image guidance during radiation delivery have markedly improved, allowing for more precisely defined treatment delivery [11].

In recent years, the use of IMRT has increased significantly. In a survey by Mell et al. [13], IMRT use increased from 32% to 73% over the years 2002 to 2004. Specifically within gynecologic cancers, IMRT utilization in 2004 was 27%. Yet many challenges remain within its integration into the field of gynecology. The purpose of this review is to discuss integration of IMRT into the treatment of cervical and endometrial cancer. IMRT is a powerful tool for the treatment of cancer with many potential clinical benefits; however, there are disadvantages that need to be recognized.

Advantages

IMRT technology [12]

IMRT differs significantly from conventional radiation planning methods. Conventional planning techniques are forward planned, where beam arrangements and beam modifications are specified, a planning point is chosen, and then a dose distribution is calculated. The plan can then be reviewed by the treating physician, and subsequent modifications can be made to adjust target coverage as well as dose to surrounding tissues.

The process of IMRT differs in many ways, and is an inverse-planning process. Target volumes and OAR volumes are defined, and then dosimetric and volumetric requirements are pre-specified. Initial beam arrangements are defined, and then multiple computer iterative calculations are performed until a mathematical solution is found which satisfies the DVH requirements. This solution is accomplished through adjustments to relative beam weight and shape, but in addition intensity modulation of each beam is performed. Within each beam, rather than a uniform and flat fluence throughout the generated aperture, as is seen in 3-D conformal plans, the fluence can be varied within individual beamlets created by MLC positioning, the sum of which then represents the entire aperture's contribution. The overlying result is that when individual contributions from each beam are summed, complex 3-dimensional dose clouds can be generated with concave shapes and steep dose gradients. This results in highly conformal treatment, where the high dose regions of the plan are confined to the target only, and doses to OARs can be minimized (see Fig. 1); however, trade-offs exist with increasing low dose to normal tissues with increasing criteria stringency.

These advances in radiation oncology have allowed for highly conformal plans that would not have previously been possible with only 3D-conformal techniques. IMRT has become standard in some disease sites, namely prostate cancer and head and neck cancer [13]; however its potential in gynecologic cancers is actively being defined.

Dosimetric advantages

There have been numerous studies that have demonstrated dosimetric benefits to IMRT in gynecologic cancers, manifested mainly in benefits to the small bowel, rectum, bladder and bone marrow [14–21]. A meta-analysis was recently conducted by Yang et al. [22], where 13 articles were reviewed in which dosimetric comparisons were made between 3D-conformal and IMRT treatment plans. A 17.3% reduction in volume of the small bowel receiving 45 Gy was seen, as well as a 39.5% reduction in rectal volumes receiving 45 Gy. No statistically significant decreases in bladder dose were seen, and while IMRT was noted to decrease volumes of bone marrow irradiated, these findings did not achieve statistical significance. However, it is worth noting that most of these studies are at least partly retrospective, with variations in relative OAR planning prioritization, so without uniform planning constraints final comparisons are difficult. In addition, bone marrow sparing was not always a prioritized OAR on these trials, again making conclusions difficult.

Clinical outcomes

Clinical toxicity

Early studies demonstrate dosimetric benefits; however, the integration of IMRT relies on improving clinical care. In one of the earliest studies to clearly demonstrate a clinical benefit, Mundt et al. [23] reported on 40 patients who underwent IMRT compared to 35 patient treated with conventional whole pelvic fields for gynecologic cancers, and noted a statistically significant reduction in grade 2 gastrointestinal toxicity. In a separate report [24] the impact on chronic gastrointestinal toxicity was reported, with a reduction in grade 2 toxicities from 16.7% to 2.8%, and grade 3 toxicity from 3.3% to 0% ($p = 0.001$). In another study by Du et al. [25], statistically significant reductions in chronic gastrointestinal and urinary toxicities were seen with the integration of IMRT compared to conventional only techniques. Other