Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Review

The role of intensity modulated radiotherapy in gynecological radiotherapy: Present and future

*Ana Fernandez-Ots, Juanita Crook**

British Columbia Cancer Agency, Center for the Southern Interior, 399 Royal Avenue, Kelowna, British Columbia, Canada V1Y 5L3

ARTICLE INFO

Article history:
Received 3 May 2013
Received in revised form
13 July 2013
Accepted 2 August 2013

Keywords:
Gynecologic malignancy
Radiotherapy
Intensity modulated radiation
Toxicity

ABSTRACT

Aim: This manuscript reviews the English language literature on the use of intensity modulated radiation therapy (IMRT) for gynecologic malignancies, focusing on the treatment cervical cancer.

Background: Radiation therapy plays a key role in both definitive and adjuvant treatment of these patients, although efforts continue to minimize acute and chronic toxicity. IMRT is an attractive option because of the potential to dose escalate to the target while sparing organs at risk.

Methods and Materials: The English language literature was reviewed for relevant studies.

Results: Multiple heterogeneous studies have showed dosimetric and clinical benefits with reduction in acute and late gastrointestinal, genitourinary and hematologic toxicity, especially in the post hysterectomy scenario and for dose escalation to para-aortic nodes. Consensus is evolving regarding necessary margins and target delineation in the context of organ movement and tumor shrinkage during the course of radiotherapy. Protocols with daily soft-tissue visualization are being investigated.

Conclusions: Consistency in approach and reporting are vital in order to acquire the data to justify the considerable increased expense of IMRT.

1. Introduction

Intensity modulated radiation therapy (IMRT) is an external beam modality which uses variable intensity across the face of the beam to shape isodoses to achieve a high tumor dose while minimizing exposure to healthy tissue. The combination of 3D planning and variable radiation intensity in each field provides dosimetric advantages which have been exploited in a variety of pathologic sites including cancer of the cervix.

Cervix cancer management varies depending on the FIGO stage, but radiotherapy plays a vital role across the range of presentations. For early stages, treatment may consist of surgery or radiotherapy alone, but in the presence of adverse prognostic factors, surgery will be combined with radiotherapy. For bulky or locally advanced presentations, combined radio-chemotherapy is the standard of care. Phase III randomized trials showing the benefit of concurrent cisplatinum with pelvic radiotherapy also provide toxicity data. Acute and chronic grade 3–4 gastrointestinal toxicity is 7–16% and

* *Corresponding author*. Tel.: +1 250 979 6645; fax: +1 250 712 3911.
E-mail address: jcrook@bccancer.bc.ca (J. Crook).

1507-1367/$ – see front matter
http://dx.doi.org/10.1016/j.rpor.2013.08.001

genitourinary up to 17%.[1–6] These toxicity rates increase when radiation fields are extended to include the para-aortic regions, with grade 3–4 acute gastrointestinal toxicity in up to 49% and chronic toxicity seen in up to 34% at 36 months. Grade 3 or 4 hematologic toxicity is reported in 76%.[1,7,8] RTOG 0116 combined chemotherapy and extended field radiotherapy, and found acute nonhematologic grade 3–4 toxicity of 81%, and chronic grade 3–4 toxicity of 40% with follow up ranging to 38 months.[7]

Follow up is relatively short in many of these studies, and despite the already high toxicity, the situation may worsen with time. Two decades ago, Eifel et al. reported that the risk of serious complications from radiotherapy increases with time but at different rates depending on the organ system studied. Retrospective analysis was performed on 1784 patients with carcinoma of the cervix treated with radiation. Grade 3 toxicity levels at 3 and 5 years were 7.7 and 9.3% but increased approximately 0.34% per year through 10–20 years. Although most serious complications are diagnosed within 2–3 years, the risk continues to increase steadily up to 25 years after treatment, especially in the genitourinary system. This underlines the need for improvement in radiotherapy delivery.[9]

2. Dosimetric benefits of IMRT

Early work on IMRT showed advantages compared to 3D conformal radiotherapy in dose reduction to the organs at risk for radiation toxicity.[10–13,14] Roeske et al. compared the dose received by the small bowel, bladder and rectum in ten patients with gynecologic cancers treated with either 3D conformal or IMRT. The V100 of the small bowel was reduced by 50% ($p = 0.0005$) and the V100 of the rectum and bladder by 23% ($p = 0.0002$ and $p = 0.0005$ respectively).[13] When IMRT is used to deliver a 20–30 Gy boost, Chan et al. found a significant reduction in high dose volumes in 12 patients with cancer of the cervix, vagina or endometrium compared to the use of 3D conformal or a 4 field box. The V66 of the rectum was reduced by 22% ($p < 0.001$) and the bladder by 19% ($p < 0.001$).[15]

Mell et al. reported the dose volume histograms for organs-at-risk for 7 patients with carcinoma of the cervix treated with chemotherapy concurrent with IMRT, 3D conformal, or an anterior-posterior parallel opposed pair and found that dose to the bone marrow and small bowel was reduced, but the reduction to the rectum and bladder was less impressive. Hematologic tolerance was improved with less grade 3–4 toxicity by reducing low-dose irradiation to the bone marrow; V20 was 99, 97.8 and 72% with AP-PA, 4-Field box, and Bone marrow sparing -IMRT.[16] The question of how much dose reduction is required, and to what volume, has not been answered. Simpson et al. suggested that a decrease in the V45 of the small bowel by 100 cc reduced grade 2 toxicity by 50% [17]. Mell et al. found a correlation between hematologic toxicity and the volume of pelvic bone marrow receiving 10–20 Gy.[16] This has been confirmed by more recent studies.[18,19]

3. Impact on toxicity

The dosimetric advantages of IMRT have resulted in reduction of both acute and chronic GI and GU toxicity.[12,20,21–25] Early retrospective studies by Mundt et al.[12,23] showed a significant decrease in acute grade 2 GU toxicity from 91 to 60%, and chronic GI toxicity from 20 to 3% with the use of IMRT rather than a 4-field box. Efforts to demonstrate superiority of IMRT over 3D conformal have produced preliminary data from many small retrospective studies with short follow up and including a heterogeneous mixture of definitive radiotherapy and post-operative patients. Doses range from 45 to 60 Gy with either pelvic or extended fields, and boosts are a mixture of brachytherapy, IMRT, or an integrated IMRT boost. Table 1 summarizes the retrospective data on toxicity.[25]

Evidence suggests that IMRT can spare bone marrow[16,26] but given the large volume of hematopoietically active marrow in the pelvis and lower lumbar spine, specific planning constraints are required. Otherwise, IMRT fails to show a clear advantage over 3D conformal, with hematologic grade 3 toxicity of 28%[21] for extended field and 24% for pelvic fields.[20]

Regarding efficacy (Table 2), no randomized comparisons of IMRT to other radiotherapy techniques exist but local failure rates, and overall and disease free survival appear to be similar for IMRT compared to 3D conformal. Haselle et al., reported on 111 cervix cancer patients with a median follow up of 27 months, treated with surgery or IMRT with or without brachytherapy. Overall survival at 3 years was 78% and disease free survival 69%.[22] Zhang et al. included only post surgical patients and consequently had only a 3.4% local regional recurrence but a 27% metastatic failure rate.[24] Overall survival at 3 years was 71% and disease free survival 66%. The most common site of failure was distant, an event that can only be reduced by improved systemic therapy.

4. IMRT planning

Traditional external beam radiotherapy is based on field limits determined by bony landmarks. Large treatment volumes include generous amounts of healthy tissue but margins of security are large, such that target motion or change in GTV during treatment are not issues. In the era of conformal treatment with steep dose gradients, definition of the GTV and CTV become crucial. Major uncertainties exist regarding IMRT for cervix cancer in determining the required margins, the acceptable degree of homogeneity and the appropriate dose limits for the organs at risk. Such contouring demands a thorough knowledge of radiologic anatomy. Current RTOG protocols using IMRT include a contouring atlas for pelvic volumes and guidelines for dosimetric constraints.

Lim et al. published treatment guidelines for the radical treatment of cervix cancer based on studies of postoperative patients to create a consensus for the CTV and PTV of the primary tumor and regional nodes. There was moderate agreement on the contours of the cervix, uterus, vagina and parametria, but determination of margins was difficult given that these structures are subject to movement, deformation and tumor regression during treatment. There was lack of agreement on the parametrial limits, the length of vagina to be included in the PTV, and whether or not to include the entire uterus. Individual variation amongst patients makes the dynamic unpredictable. Margins of 1.5–2 cm around the tumor CTV and 7 mm around the PTV were suggested, but only