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Methods, safety, and early clinical outcomes of dose escalation using simultaneous integrated and sequential boosts in patients with locally advanced gynecologic malignancies

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HIGHLIGHTS

- Patients were treated with dose escalated radiotherapy using simultaneous integrated and sequential boosts to doses up to 65 Gy.
- This technique is demonstrated to be safe with acceptable rates of acute and late toxicities.
- Early rates of local control are favorable suggesting a benefit to patients of this treatment approach.

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ABSTRACT

Objective. To evaluate the safety of dose escalated radiotherapy using a simultaneous integrated boost technique in patients with locally advanced gynecological malignancies.

Methods. Thirty-nine women with locally advanced gynecological malignancies were treated with intensity modulated radiation therapy utilizing a simultaneous integrated boost (SIB) technique for gross disease in the para-aortic and/or pelvic nodal basins, sidewall extension, or residual primary disease. Women were treated to 45 Gy in 1.8 Gy fractions to elective nodal regions. Gross disease was simultaneously treated to 55 Gy in 2.2 Gy fractions (n = 44 sites). An additional sequential boost of 10 Gy in 2 Gy fractions was delivered if deemed appropriate (n = 29 sites). Acute and late toxicity, local control in the treated volumes (LC), overall survival (OS), and distant metastases (DM) were assessed.

Results. All were treated with a SIB to a dose of 55 Gy. Twenty-four patients were subsequently treated with a sequential boost to a median dose of 65 Gy. Median follow-up was 18 months. Rates of acute > grade 2 gastrointestinal (GI), genitourinary (GU), and hematologic (heme) toxicities were 2.5%, 0%, and 30%, respectively. There were no grade 4 acute toxicities. At one year, grade 1–2 late GI toxicities were 24.5%. There were no grade 3 or 4 late GI toxicities. Rates of grade 1–2 late GU toxicities were 12.7%. There were no grade 3 or 4 late GU toxicities.

Conclusion. Dose escalated radiotherapy using a SIB results in acceptable rates of acute toxicity.

Introduction

Treatment of the pelvic and para-aortic lymph node basins has long been used in the treatment of gynecologic malignancies. Early trials investigating the role of prophylactic extended field radiation therapy (EFRT) to the para-aortic nodal basins showed improved oncologic outcomes [1] but also reported an attendant increase in the risk of toxicity [2]. In an early trial conducted by the Radiation Therapy Oncology Group (RTOG), there was an 8% risk of grade 4 or 5 toxicity with EFRT compared to 4% in the pelvic radiation only arm [1]. Of note the study did not include the use of concurrent chemotherapy. In the update of RTOG 90-01, a study of chemoradiation where EFRT without chemotherapy was employed in the control arm, 12% of patients receiving EFRT experienced grade 3 or 4 late toxicity [2].

Therapeutic EFRT with concurrent chemotherapy has also been utilized in patients with para-aortic nodes involved by metastatic disease. Early phase II studies of EFRT with chemotherapy were conducted by both the Gynecologic Oncology Group (GOG) and RTOG, both demonstrating high rates of acute toxicities with concurrent chemoradiation and EFRT [3,4]. In GOG 125, the rate of acute grade 3–4 toxicities was 15.1% [3] while in RTOG 9210, the rate of acute grade 4 bowel toxicity was 28% [4]. A more recent phase 2 trial, RTOG 0116, investigated EFRT with concurrent cisplatin for patients with involved para-aortic nodes, employing doses to clinically involved nodal disease up to

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59.4 Gy [5]. Acute gastrointestinal (GI) toxicities were high with reported rates of toxicity grade ≥3 in 34.6% of patients.

Techniques for delivering radiation, such as intensity modulated radiation therapy (IMRT), have been employed in multiple settings to reduce radiation dose to organs at risk and subsequent treatment related toxicity. There is data to suggest that delivery of EFRT using IMRT (EF–IMRT) may reduce the incidence of acute and late GI toxicities [6,7]. Available literature suggests that a dose response exists in terms of lymph node control [8]. Subsequent data has demonstrated the safety of dose-escalation using EF–IMRT with concurrent chemotherapy [9,10]. This approach has resulted in high rates of local control as well as exceedingly low rates of late toxicity [11].

A simultaneous integrated boost (SIB, also termed 'dose-painting') is a novel technique, in which boost volumes such as involved nodes, receive a higher dose per fraction (e.g. 2.2 Gy per day) within a larger volume receiving a lower dose (e.g. 1.8 Gy per day) via intentional dose heterogeneity. This is in part due to the reduced dose gradient required when building from 1.8 Gy to 2.2 Gy (18% increase) than the 75–80% dose gradient required for equivalent sparing if the boost is given sequentially after standard therapy. Use of a SIB also results in a reduction in overall treatment time limiting tumor repopulation, and delivery of a higher dose per fraction resulting in a higher biologically equivalent dose (BED). Using the linear quadratic model to correct for fraction size and reduced treatment time, a SIB plan using 2.2 Gy/day to a total dose of 55 Gy is equivalent to a sequential boost of 1.8 Gy/day to a total dose of 64.8 Gy [12]. The higher dose per fraction however may result in unpredicted acute or late toxicity due to the non-standard fraction size, particularly if normal tissue unexpectedly enters the SIB boost volume.

In this retrospective analysis, we sought to evaluate the safety of dose escalated EF–IMRT using a SIB technique.

Methods and materials

Between 2009 and 2012 39 patients with locally advanced gynecological malignancies were treated with IMRT utilizing a SIB technique. All charts were retrospectively reviewed with institutional review board approval. All women were treated to a dose of 45 Gy in 1.8 Gy fractions to lymph node regions at risk. Site of gross disease, either lymph node metastases or pelvic sidewall extension, were treated to a dose of 55 Gy using 2.2 Gy fractions, given simultaneously with the 1.8 Gy fractions. In certain clinical situations, an additional sequential boost was delivered to gross disease at the discretion of the treating radiation oncologist. Brachytherapy was preferred to boost uterine, cervical or vaginal disease, and therefore these areas were limited to 1.8 Gy per fraction, resulting in a cumulative dose of 45 Gy. Daily on board imaging was used in all patients for kV to kV daily image matching to the pelvis and the lumbosacral spine. Cone beam computed tomography (CBCT) was performed on fractions 1, 2, 5, and 15 at minimum, to verify the reliability of the kV to kV daily matching, and that adjacent normal tissue location was maintained. If indicated, plans were revised to account for inter-fraction variations, and additional regular CBCTs were obtained to confirm a reproducible setup.

Target structures included the gross tumor, and para-aortic, and pelvic lymph nodes as clinically indicated. Nodal target volumes were contoured based on RTOG guidelines [13]. For definitive treatment of uterine or cervical cancers, a planning MRI was obtained and the more recent RTOG guidelines were used [14]. Our policy for nodal CTV delineation was to include one nodal echelon above the highest clinically involved nodes. Organs at risk (OARs), where appropriate, including the bladder, small bowel, rectum, kidneys, and sigmoid colon were contoured. Treatment plans utilizing IMRT or volumetric arc modulated radiation therapy (VMAT) were generated using Eclipse software (Varian Medical Systems, Palo Alto, CA). The following general OAR constraints were used during planning: the volume of small bowel exceeding 55 Gy, the volume of sigmoid exceeding 58 Gy, and the volumes of the rectum and bladder exceeding 110% of the prescription dose, were limited to less than 2 ml (i.e. D2cc small bowel < 55 Gy, D2cc Sigmoid < 58 Gy, and D2cc rectum/bladder < 110% of the prescription). Additionally, the volume of the kidneys receiving >18 Gy was limited to 15–30%. After these constraints were met, coverage of the PTV was prioritized and doses to OARs were minimized.

Dose volume histograms (DVH) were generated for all OARs. For this analysis, the minimum dose within the 2 cm^3 volume receiving the highest dose (D2cc), for the bladder, small bowel, rectum, and sigmoid colon were captured for correlation to acute and late toxicity. Also collected were the minimum doses to the following volumes of organs receiving the highest dose: 35% of the bladder (D35), 30% of the small bowel (D30), and 60% of the rectum (D60). These dosimetric endpoints were selected in accordance with RTOG suggested constraints for pelvic IMRT [15].

During the course of radiation therapy, patients were evaluated weekly to assess treatment-related morbidity as per standard practice. Toxicity was scored as acute if within 90 days of the completion of radiotherapy and as late thereafter. All toxicities were scored by the National Cancer Institute Toxicity Criteria for Adverse Events, version 4.0. Patients were alternatively assessed by a radiation oncologist and gynecologic oncologists at 3-month intervals for the assessment of treatment-related morbidity and for disease persistence or recurrence.

All statistical analyses were performed using IBM SPSS v20 (New York, NY). The Kaplan–Meier method was utilized to calculate rates of late toxicities as well as all disease specific outcomes. All statistical tests were 2-tailed.

Results

The characteristics of the study population are displayed in Table 1. The majority of patients had a primary cervical cancer (n = 22), all treated with definitive chemoradiation. Eight patients with endometrial cancer were included, four of whom were inoperable and four of whom had nodal recurrence. Five patients had vulvar cancer with nodal involvement. All three ovarian cancer patients were treated for nodal recurrence in the absence of peritoneal disease.

Of the 26 patients who received concurrent chemotherapy, all received cisplatin with the exception of one who received carboplatin. The most common regimen was cisplatin 40 mg/m^2 administered weekly during radiation. Twenty-four patients had their primary disease boosted by intracavitary brachytherapy utilizing a high-dose rate in all but one patient. The disease sites receiving a SIB as well as those receiving a SIB followed by sequential boost are presented in Table 2. The most common sites to be treated by a SIB were sidewall extension

Table 1
Patient characteristics.

Characteristic	N
No. of patients	39
Age	
Mean	59.3
Range	30–82
Tumor site	
Cervical	22
Endometrial	4
Recurrent endometrial	5
Vulvar	5
Recurrent ovarian	3
Chemotherapy	
Cisplatin	25
Carboplatin	1
None	13
Brachytherapy	
Yes	24
No	15