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Review

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

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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

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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

Table 1 – Retrospective studies on toxicity comparing IMRT to other RT techniques.

Author/year	*n*	Patients	Technique	Field	Planning target volume	Dose	Follow-up (median)	Acute toxicity	Chronic toxicity	*p*-Value
Mundt 2002[12]	40	Cervix/Endo[a]	EBRT 4F[b] vs IMRT[c]	Pelvic	CTV[d] + 1 cm	45 Gy	NS	GI[e] gr2: 60% GU[f] gr2 10% No G3	na	$p = 0.002$ $p = 0.22$ Reduced Tox[g] G2 for IMRT vs EBRT 4F
Mundt 2003[23]	36	Cervix/Endo I-II 70% RT Adjuvant	EBRT 4F vs IMRT	Pelvic	CTV + 1 cm	45 Gy	19 m	N/A	GI 19% grade not specified	$p = 0.001$ Reduced Tox compared to 3Dc[h]
Chen 2007[11]	68	Cervix RT Adjuvant	EBRT4F vs IMRT+ CT[i]	Pelvic	na	50.4 Gy	14 m	GI 1–2 36% GU 1–2 30%	GI 6% GU 9%	$p < 0.05$, but Late Tox GU $p = 0.231$
Beriwal 2007[21]	36	Cervix RT Adjuvant Ib2-IVa	IMRT+ HDR-BT[j] + CT	Pelvic + para[k]	CTV 0.5 + 1 cm	45 Gy	18 m	GI gr 3:3% GU gr 3:3%	GU 3% Grade ≥3 2y-actuarial 10%	
Kidd 2010[25]	452	Cervix Ia-IVb	PET-CT guided IMRT+ HDR vs RTC3D + HDR/LDR[l] + CT	PET positive para, pelvic + para	CTV +7 mm	50.4 Gy	52 m	NA	G3 GU or GI IMRT 6% 3Dc 17%	$p = 0.0017$
Chen 2011[20]	109	Cervix IB2-IVA	IMRT + BT + CT	Pelvic	CTV + 0.7–1 cm	50.4–54 Gy	32 m	GI 3:3%	GI 4.5%	
Hasselle 2011[22]	111	Cervix I-IVA Radical and Adjuvant	IMRT + HDR – BT CT	Pelvic	CTV + 0.7–1 cm	45 Gy	27 m	Grade ≥3 2%	Late tox $g > = 3$:7%	
Zhang 2012[24]	58	Cervix I-II Adjuvant	IMRT + QT	Pelvic + Para	CTV +1CM	50.4 Gy	34 m	GU/GI G3 tox 5%	RTOG toxicity G3 5.1%	

[a] Endometrium.
[b] External beam radiotherapy 4 fields.
[c] Intensity modulated radiation therapy.
[d] Clinical target volume.
[e] Gastrointestinal.
[f] Genitourinary.
[g] Toxicity.
[h] Radiotherapy conformal 3D.
[i] Chemotherapy.
[j] High dose rate brachytherapy.
[k] Paraortic field.
[l] Low dose rate brachytherapy.

Table 2 – Results for pelvic Irradiation with IMRT in terms of local failure, disease free survival, and overall survival.

Author/year	*n*	Patients	Technique	Field	Planning target volume	Dose	Follow-up (median)	Local failure	Distant failure
Chen 2007[11]	68	Cervix Adjuvant	4F[b] vs IMRT[a]	Pelvic	na	50.4 Gy	14 m	EBRT: 4F 6% IMRT: 7%	
Beriwal 2007[21]	36	Cervix Ib2-IVa	IMRT	Pelvic + para[c]	CTV 0.5 + 1 cm	45 Gy	18 m		
Kidd 2010[25]	452	Cervix Ia-IVb PET CT staging	IMRT or 3Dc + HDR/LDR	PET positive Para, pelvic+ para	CTV[d] +7 mm	50.4 Gy	52 m	IMRT 8.1% 3Dc[e] 10.4% *p* value ns	IMRT 15.6% 3Dc 24.6% *p* value ns
Chen 2011[20]	109	Cervix IB2-IVA	IMRT + BT[f]	Pelvic	CTV + 0.7–1 cm	50.4–54 Gy	32 m	13.8% 3 years	22%
Hasselle 2011[22]	111	Cervix I-IVA Radical and Adjuvant	IMRT + HDR – BT[g]	Pelvic	CTV + 0.7–1 cm	45 Gy	27 m	14%@ 3 years	17% @ 3years
Zhang 12[24]	58	Cervix I-II Adjuvant	IMRT – Para	Pelvic + Para	CTV +1 cm	50.4 Gy	34 m	3.4%	27%

[a] Intensity modulated radiation therapy.
[b] External beam radiotherapy 4 fields.
[c] Paraortic field.
[d] Clinical target volume.
[e] 3D conformal.
[f] Brachytherapy.
[g] High dose rate brachytherapy.

with daily soft tissue visualization for position verification. If bony landmarks are used for set-up, then margins must be more generous.[27]

Several studies have shown the importance of cervical tumor regression during treatment, with a median volume reduction of 46% (range: 6–100%).[14,28] This suggests that IMRT should be replanned during the final third of treatment to take advantage of the shrinking GTV. However, the reduction in the CTV and PTV may be disproportionally small. Van de Bunt et al. imaged 14 patients with MRI during treatment and reported that when GTV reduction exceeded 30 cc, re-planning reduced the small bowel in the high dose volume significantly. Margins of 10–15 mm were acceptable.[14] Similarly, Lim et al. confirmed that DVH's did not accurately reflect the actual dose received by the target and organs at risk due to reduction in the GTV of 48–96% and CTV of 8–77% in 20 patients imaged weekly with MRI. He compared 3 IMRT plans with different margins and concluded that a margin of 5 mm may be adequate provided daily soft tissue visualization was used for treatment set up.[27]

In addition to tumor regression, cervical-utero movement is also an issue in IMRT delivery. Margins for this mobile target are at variance with those required for the relatively fixed nodal CTV. Taylor et al. imaged 33 patients with gynecologic cancer using MRI and confirmed that since the uterus is more mobile than the cervix, asymmetric margins may be more appropriate.[29] Gordon et al. looked at 3 different dynamic models for the utero-cervical unit and concluded that the uterus would be under-dosed if margins were chosen based on cervical movement.[30] The bladder, rectum and small bowel are also dynamic mobile structures that effect the position of the GTV.[31–33] Protocols requiring a full bladder and empty rectum can minimize utero-cervical movement; such requirements are included in recent RTOG protocols.[34] The development of individualized strategies is essential due to the large variation within and between fractions for each patient. New protocols are being tested based on imaging techniques that deal with the variation in these structures during treatment, such as MRI, bladder ultrasound and CT.[31–33]

Aside from under-dosing the target because of organ movement, tumor regression and inaccurate contouring, there are other significant risks to take into consideration with IMRT. Due to the multiplicity of fields and delivery angles, the integral dose to the patient is much higher than with other techniques (Fig. 1). Studies such as MEII08 suggest that the volume of healthy tissue such as the small intestine, rectum and bladder receiving a very low dose of radiation was higher with IMRT.[16] This may lead to development of radiation induced malignancy.[35–37]

5. IMRT and its impact on resources

The complexity of IMRT results in greater consumption of resources compared to traditional radiation techniques. The time required for physicist and oncologist to complete contouring tasks and treatment planning is much greater due to the detail required in contouring and the number of fields employed. To minimize positioning errors, immobilization must be certain and precise, and therapists take longer to position patients. IMRT demands more expensive and

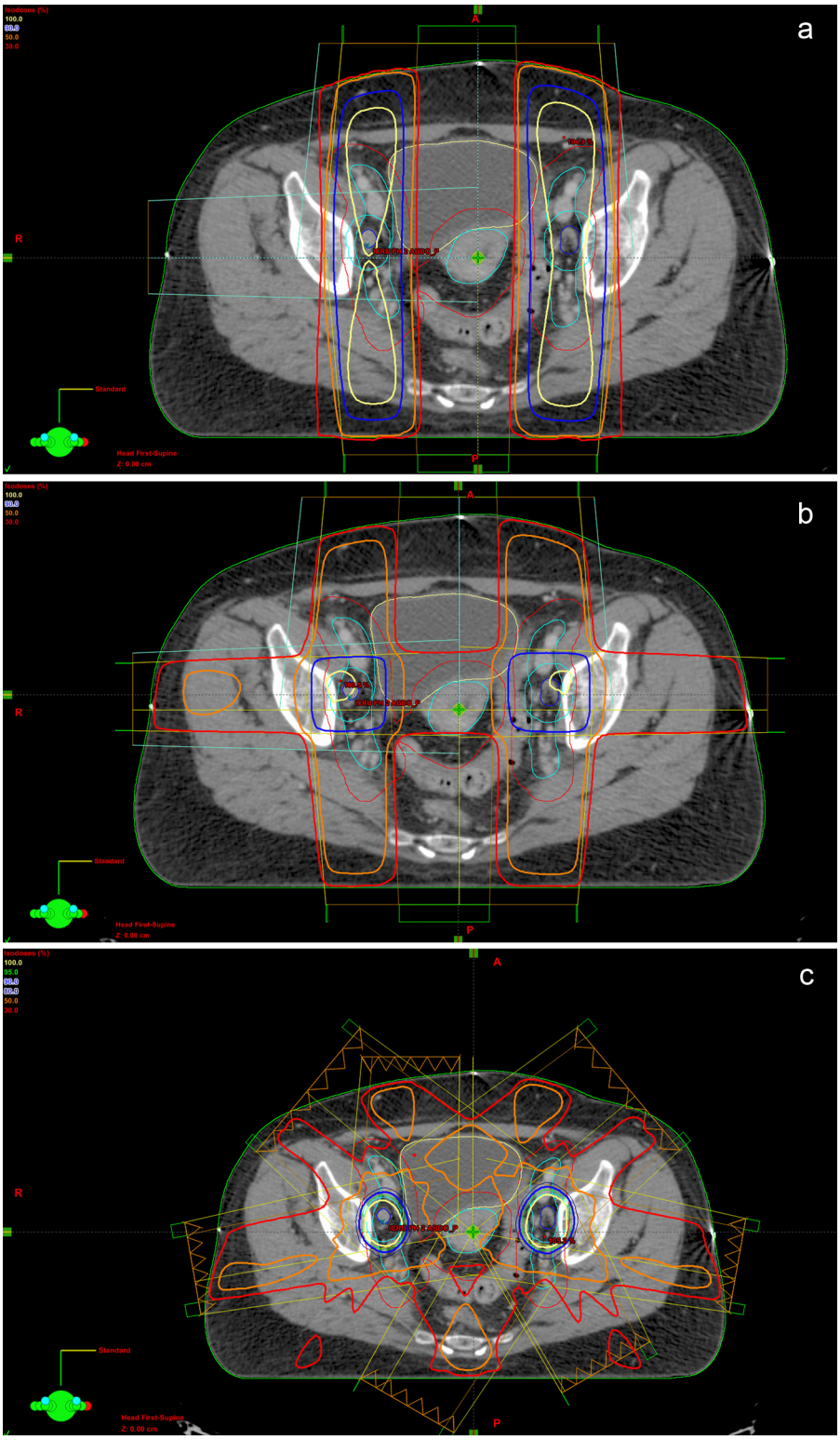

Fig. 1 – Comparison of nodal boost plans, with respect to integral dose to the patient and the volume of tissue receiving low level radiation. (a) Parallel opposed pair plan. (b) 4-FIELD plan. (c) IMRT plan. Note the extensive volume enclosed by the 30% isodose in plan c.

sophisticated planning systems, quality control and maintenance protocols. Recent analyses of cost effectiveness comparing IMRT with 3D conformal for tumor sites such as prostate and head and neck have shown that the use of IMRT for prostate cancer in the United States increased the cost for each quality adjusted life year saved by $50,000 compared 3D conformal.[38,39] In Canada, the increased expense is $27,800 over alternative techniques. In Spain IMRT costs 5–6 times

more than 3D conformal. The variation between countries depends on health care billing practices and the details of how IMRT is performed.

6. The current role of IMRT

Dose escalation to the pelvis and para-aortic region with conventional radiotherapy is prohibited by unacceptable toxicity.[8] The dosimetric benefits of IMRT have been concentrated in delivering a boost to these regions or a central boost to patients not suitable for brachytherapy. Simultaneous boosts to the target or affected lymph nodes have shown good results and the altered fractionation of a simultaneous boost has the advantage of shortening treatment time and improving the therapeutic ratio.[15,40]

At present the role and potential benefits of IMRT have been best established in the setting of post operative treatment thanks to the findings of RTOG 0418.[34] In 2008 Small et al. published guidelines for contouring post operative patients to establish consistency of reporting amongst institutions for ease of comparison of data.[41] Preliminary results from individual institutions have shown a benefit for these guidelines for both early stage disease as well as for those with positive nodes.[11,24,42] The advantage of IMRT for sparing of bone marrow in patients treated for pelvic tumors are being achieved by identifying specifically the active marrow in the treatment field using PET, MRI or SPECT. Early results are promising.[43–45]

7. Future directions

Improvements in toxicity allow evaluation of more aggressive treatment approaches. Dueñas Gonzalez has reported good results with more radical chemotherapy in locally advanced cervix cancer.[46]

One of the more important advances in the last decade has been identification of genetic variability in the individual response to radiotherapy through genetic markers of radiation toxicity. Single nucleotide polymorphisms (SNP's) are variations in the gene sequence that effect a single base pair and appear in at least 1% of the population. There are 11.8 million SNP's registered in the NCBI genome data base. Numerous studies are focusing on phenotypes susceptible to cancer and to radiation toxicity. Phenotypic expression is complex and is influenced by many life style and environmental factors. There are not yet any consistent associations between certain SNP's and types of radiation toxicity, possibly because of the great number of treatment variables that are also known to influence toxicity, such as the type of radiation, dose, treatment volume, fractionation and use of concurrent chemotherapy. Research in this area is just beginning.[47]

8. Conclusions

IMRT offers dosimetric advantages in organ sparing compared with traditional 2D or 3D radiotherapy in treatment of cancer of the cervix. This has maintained excellent long term cure rates while reducing GI, GU and hematologic toxicity, especially in patients treated with concurrent chemotherapy. IMRT has made possible safer dose escalation to the para-aortic region, or bulky GTV in patients nor suitable for brachytherapy. However, these results should be taken with some caution given the heterogeneity of the populations studied, the small numbers of patients, short follow up and great variability in margins, treatment fields and dose prescription. A multi center study has shown that the use of IMRT for postoperative cases is reliable, but a clear consensus is still lacking for the delivery of radical treatment. Recommendations for contouring of volumes and the required margins continue to be debated, given the inherent complexity of the pelvic dynamic, the movement and regression of the tumor and variable size and position of the neighboring organs. In addition to contouring and planning issues, daily treatment verification must include soft tissue imaging to ensure correct alignment on the target.

IMRT is a high complex modality with an infinite number of planning options regarding the number of fields and angles of incidence to cover the required volumes and to meet the dose restrictions for the organs at risk. The result is both a flexible and powerful tool but one which consumes vast resources in terms of physics, physicians, therapists and machine time. Further prospective multi center trials will provide the required data on disease control, toxicity and quality of life to fully integrate IMRT into the management of cervical cancer.

Conflict of interest

None declared.

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REFERENCES

1. Eifel PJ, Winter K, Morris M, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. *J Clin Oncol* 2004;**22**(5):872–80, http://dx.doi.org/10.1200/JCO.2004.07.197.
2. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a gynecologic oncology group and southwest oncology group study. *J Clin Oncol* 1999;**17**(5):1339–48.
3. Rose PG, Ali S, Watkins E, et al. Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a gynecologic oncology group study. *J Clin Oncol* 2007;**25**(19):2804–10, http://dx.doi.org/10.1200/JCO.2006.09.4532.
4. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999;**340**(15):1144–53, http://dx.doi.org/10.1056/NEJM199904153401502.

5. Stehman FB, Ali S, Keys HM, et al. Radiation therapy with or without weekly cisplatin for bulky stage 1B cervical carcinoma: follow-up of a gynecologic oncology group trial. *Am J Obstet Gynecol* 2007;**197**(5), http://dx.doi.org/10.1016/j.ajog.2007.08.003, 503.e1–503.e6.
6. Peters 3rd WA, Liu PY, Barrett 2nd RJ, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol* 2000;**18**(8):1606–13.
7. Small Jr W, Winter K, Levenback C, et al. Extended-field irradiation and intracavitary brachytherapy combined with cisplatin and amifostine for cervical cancer with positive para-aortic or high common iliac lymph nodes: results of arm II of radiation therapy oncology group (RTOG) 0116. *Int J Gynecol Cancer* 2011;**21**(7):1266–75, http://dx.doi.org/10.1097/IGC.0b013e31822c2769.
8. Grigsby PW, Heydon K, Mutch DG, Kim RY, Eifel P. Long-term follow-up of RTOG 92-10: Cervical cancer with positive para-aortic lymph nodes. *Int J Radiat Oncol Biol Phys* 2001;**51**(4):982–7.
9. Eifel PJ, Levenback C, Wharton JT, Oswald MJ. Time course and incidence of late complications in patients treated with radiation therapy for FIGO stage IB carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 1995;**32**(5):1289–300, http://dx.doi.org/10.1016/0360-3016(95)00118-I.
10. Portelance L, Chao KS, Grigsby PW, Bennet H, Low D. Intensity-modulated radiation therapy (IMRT) reduces small bowel, rectum, and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation. *Int J Radiat Oncol Biol Phys* 2001;**51**(1):261–6.
11. Chen MF, Tseng CJ, Tseng CC, Kuo YC, Yu CY, Chen WC. Clinical outcome in posthysterectomy cervical cancer patients treated with concurrent cisplatin and intensity-modulated pelvic radiotherapy: comparison with conventional radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;**67**(5):1438–44, http://dx.doi.org/10.1016/j.ijrobp.2006.11.005.
12. Mundt AJ, Lujan AE, Rotmensch J, et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2002;**52**(5):1330–7.
13. Roeske JC, Lujan A, Rotmensch J, Waggoner SE, Yamada D, Mundt AJ. Intensity-modulated whole pelvic radiation therapy in patients with gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2000;**48**(5):1613–21.
14. van de Bunt L, van der Heide UA, Ketelaars M, de Kort GA, Jurgenliemk-Schulz IM. Conventional, conformal, and intensity-modulated radiation therapy treatment planning of external beam radiotherapy for cervical cancer: the impact of tumor regression. *Int J Radiat Oncol Biol Phys* 2006;**64**(1):189–96, http://dx.doi.org/10.1016/j.ijrobp.2005.04.025.
15. Chan P, Yeo I, Perkins G, Fyles A, Milosevic M. Dosimetric comparison of intensity-modulated, conformal, and four-field pelvic radiotherapy boost plans for gynecologic cancer: a retrospective planning study. *Radiat Oncol* 2006;**1**:13, http://dx.doi.org/10.1186/1748-717X-1-13.
16. Mell LK, Tiryaki H, Ahn KH, Mundt AJ, Roeske JC, Aydogan B. Dosimetric comparison of bone marrow-sparing intensity-modulated radiotherapy versus conventional techniques for treatment of cervical cancer. *Int J Radiat Oncol Biol Phys* 2008;**71**(5):1504–10, http://dx.doi.org/10.1016/j.ijrobp.2008.04.046.
17. Simpson DR, Song WY, Moiseenko V, et al. Normal tissue complication probability analysis of acute gastrointestinal toxicity in cervical cancer patients undergoing intensity modulated radiation therapy and concurrent cisplatin. *Int J Radiat Oncol Biol Phys* 2012;**83**(1):e81–6, http://dx.doi.org/10.1016/j.ijrobp.2011.12.012.
18. Rose BS, Aydogan B, Liang Y, et al. Normal tissue complication probability modeling of acute hematologic toxicity in cervical cancer patients treated with chemoradiotherapy. *Int J Radiat Oncol Biol Phys* 2011;**79**(3):800–7, http://dx.doi.org/10.1016/j.ijrobp.2009.11.010.
19. Albuquerque K, Giangreco D, Morrison C, et al. Radiation-related predictors of hematologic toxicity after concurrent chemoradiation for cervical cancer and implications for bone marrow-sparing pelvic IMRT. *Int J Radiat Oncol Biol Phys* 2011;**79**(4):1043–7, http://dx.doi.org/10.1016/j.ijrobp.2009.12.025.
20. Chen CC, Lin JC, Jan JS, Ho SC, Wang L. Definitive intensity-modulated radiation therapy with concurrent chemotherapy for patients with locally advanced cervical cancer. *Gynecol Oncol* 2011;**122**(1):9–13, http://dx.doi.org/10.1016/j.ygyno.2011.03.034.
21. Beriwal S, Gan GN, Heron DE, et al. Early clinical outcome with concurrent chemotherapy and extended-field, intensity-modulated radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2007;**68**(1):166–71, http://dx.doi.org/10.1016/j.ijrobp.2006.12.023.
22. Hasselle MD, Rose BS, Kochanski JD, et al. Clinical outcomes of intensity-modulated pelvic radiation therapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2011;**80**(5):1436–45, http://dx.doi.org/10.1016/j.ijrobp.2010.04.041.
23. Mundt AJ, Mell LK, Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. *Int J Radiat Oncol Biol Phys* 2003;**56**(5): 1354–60.
24. Zhang G, Fu C, Zhang Y, et al. Extended-field intensity-modulated radiotherapy and concurrent cisplatin-based chemotherapy for postoperative cervical cancer with common iliac or para-aortic lymph node metastases: a retrospective review in a single institution. *Int J Gynecol Cancer* 2012;**22**(7):1220–5, http://dx.doi.org/10.1097/IGC.0b013e3182643b7c.
25. Kidd EA, Siegel BA, Dehdashti F, et al. Clinical outcomes of definitive intensity-modulated radiation therapy with fluorodeoxyglucose-positron emission tomography simulation in patients with locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys* 2010;**77**(4):1085–91, http://dx.doi.org/10.1016/j.ijrobp.2009.06.041.
26. Mell LK, Kochanski JD, Roeske JC, et al. Dosimetric predictors of acute hematologic toxicity in cervical cancer patients treated with concurrent cisplatin and intensity-modulated pelvic radiotherapy. *Int J Radiat Oncol Biol Phys* 2006;**66**(5):1356–65, http://dx.doi.org/10.1016/j.ijrobp.2006.03.018.
27. Lim K, Small Jr W, Portelance L, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer. *Int J Radiat Oncol Biol Phys* 2011;**79**(2):348–55, http://dx.doi.org/10.1016/j.ijrobp.2009.10.075.
28. Lim K, Kelly V, Stewart J, et al. Pelvic radiotherapy for cancer of the cervix: is what you plan actually what you deliver? *Int J Radiat Oncol Biol Phys* 2009;**74**(1):304–12, http://dx.doi.org/10.1016/j.ijrobp.2008.12.043.
29. Taylor A, Powell ME. An assessment of interfractional uterine and cervical motion: Implications for radiotherapy target volume definition in gynaecological cancer. *Radiother Oncol* 2008;**88**(2):250–7, http://dx.doi.org/10.1016/j.radonc.2008.04.016.
30. Gordon JJ, Weiss E, Abayomi OK, Siebers JV, Dogan N. The effect of uterine motion and uterine margins on target and normal tissue doses in intensity modulated radiation therapy

of cervical cancer. *Phys Med Biol* 2011;**56**(10):2887–901, http://dx.doi.org/10.1088/0031-9155/56/10/001.
31. Ahmad R, Hoogeman MS, Bondar M, et al. Increasing treatment accuracy for cervical cancer patients using correlations between bladder-filling change and cervix-uterus displacements: proof of principle. *Radiother Oncol* 2011;**98**(3):340–6, http://dx.doi.org/10.1016/j.radonc.2010.11.010.
32. Bondar L, Hoogeman M, Mens JW, et al. Toward an individualized target motion management for IMRT of cervical cancer based on model-predicted cervix-uterus shape and position. *Radiother Oncol* 2011;**99**(2):240–5, http://dx.doi.org/10.1016/j.radonc.2011.03.013.
33. Bondar ML, Hoogeman MS, Mens JW, et al. Individualized nonadaptive and online-adaptive intensity-modulated radiotherapy treatment strategies for cervical cancer patients based on pretreatment acquired variable bladder filling computed tomography scans. *Int J Radiat Oncol Biol Phys* 2012;**83**(5):1617–23, http://dx.doi.org/10.1016/j.ijrobp.2011.10.011.
34. Portelance L, Winter K, Jhingran A, et al. Post-operative pelvic intensity modulated radiation therapy (IMRT) with chemotherapy for patients with cervical Carcinoma/RTOG 0418 phase II study. *Int J Radiat Oncol Biol Phys* 2009;**75**(3):S640–1. http://linkinghub.elsevier.com/retrieve/pii/S0360301609025048?showall=true
35. Hall EJ, Wuu CS. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. *Int J Radiat Oncol Biol Phys* 2003;**56**(1):83–8.
36. Hall EJ. Intensity-modulated radiation therapy protons, and the risk of second cancers. *Int J Radiat Oncol Biol Phys* 2006;**65**(1):1–7, http://dx.doi.org/10.1016/j.ijrobp.2006.01.027.
37. Kry SF, Salehpour M, Followill DS, et al. The calculated risk of fatal secondary malignancies from intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2005;**62**(4):1195–203, http://dx.doi.org/10.1016/j.ijrobp.2005.03.053.
38. Konski A, Watkins-Bruner D, Feigenberg S, et al. Using decision analysis to determine the cost-effectiveness of intensity-modulated radiation therapy in the treatment of intermediate risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2006;**66**(2):408–15, http://dx.doi.org/10.1016/j.ijrobp.2006.04.049.
39. Yong JH, Beca J, McGowan T, Bremner KE, Warde P, Hoch JS. Cost-effectiveness of intensity-modulated radiotherapy in prostate cancer. *Clin Oncol (R Coll Radiol)* 2012;**24**(7):521–31, http://dx.doi.org/10.1016/j.clon.2012.05.004.
40. Kavanagh BD, Schefter TE, Wu Q, et al. Clinical application of intensity-modulated radiotherapy for locally advanced cervical cancer. *Semin Radiat Oncol* 2002;**12**(3):260–71, http://dx.doi.org/10.1053/srao.2002.32471.
41. Small Jr W, Mell LK, Anderson P, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. *Int J Radiat Oncol Biol Phys* 2008;**71**(2):428–34, http://dx.doi.org/10.1016/j.ijrobp.2007.09.042.
42. Folkert MR, Shih KK, Abu-Rustum NR, et al. Postoperative pelvic intensity-modulated radiotherapy and concurrent chemotherapy in intermediate- and high-risk cervical cancer. *Gynecol Oncol* 2013;**128**(2):288–93, http://dx.doi.org/10.1016/j.ygyno.2012.11.012.
43. Liang Y, Bydder M, Yashar CM, et al. Prospective study of functional bone marrow-sparing intensity modulated radiation therapy with concurrent chemotherapy for pelvic malignancies. *Int J Radiat Oncol Biol Phys* 2013;**85**(2):406–14, http://dx.doi.org/10.1016/j.ijrobp.2012.04.044.
44. Mahantshetty U, Krishnatry R, Chaudhari S, et al. Comparison of 2 contouring methods of bone marrow on CT and correlation with hematological toxicities in non-bone marrow-sparing pelvic intensity-modulated radiotherapy with concurrent cisplatin for cervical cancer. *Int J Gynecol Cancer* 2012;**22**(8):1427–34, http://dx.doi.org/10.1097/IGC.0b013e3182664b46.
45. Roeske JC, Lujan A, Reba RC, Penney BC, Diane Yamada S, Mundt AJ. Incorporation of SPECT bone marrow imaging into intensity modulated whole-pelvic radiation therapy treatment planning for gynecologic malignancies. *Radiother Oncol* 2005;**77**(1):11–7, http://dx.doi.org/10.1016/j.radonc.2005.06.017.
46. Duenas-Gonzalez A, Zarba JJ, Patel F, et al. Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. *J Clin Oncol* 2011;**29**(13):1678–85, http://dx.doi.org/10.1200/JCO.2009.25.9663.
47. Alsner J, Andreassen CN, Overgaard J. Genetic markers for prediction of normal tissue toxicity after radiotherapy. *Semin Radiat Oncol* 2008;**18**(2):126–35, http://dx.doi.org/10.1016/j.semradonc.2007.10.004.