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ORIGINAL ARTICLE **CME**

Better Technology But Similar Outcomes: Lessons from the University of Florida Experience with Primary Radiotherapy for Early-stage Cervix Cancer

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ABSTRACT

Objective: *To determine if the use of more complex technology in the form of 3-dimensional treatment planning improved outcomes after primary radiotherapy for early-stage cervical cancer.*

Methods: *180 Consecutive cases treated with primary radiotherapy from 1980 to 2005 for stage IB to IIB cancer of the cervix were reviewed. In 1996, we increased the cost and complexity of the planning process by changing from 2-dimensional to 3-dimensional treatment planning. The purpose of this project was to test the hypothesis that such change in treatment planning improved patient outcome.*

Results: *3-Dimensional planning was not associated with better outcomes as measured by relapse-free survival or grade 3-5 toxicity.*

Conclusion: *At our institution, converting to 3-dimensional radiotherapy planning for cervix cancer increased the cost and complexity of treatment without improving outcomes. This observation has important implications for the implementation of new technologies beyond settings where efficacy has been clearly demonstrated.*

Key Words: *Radiotherapy, conformal; Tomography, X-ray computed; Treatment outcome; Uterine cervical neoplasms*

中文摘要

技術改善但結果類似：佛羅里達大學對首次放射治療早期子宮頸癌的經驗

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目的：探討利用較複雜的三維治療計劃技術能否改善首次放射治療早期子宮頸癌的療效。

方法：回顧1980年至2005年IB至IIB期子宮頸癌共180個連續病例。從1996年開始，由於由二維治療計劃改為三維治療設計，因此增加了治療成本及設計的複雜性。本研究旨在測試此改變能改善治療結果這一假設是否正確。

結果：利用無復發生存率及3至5級毒性反應作結果測量，發現三維式治療計劃並無改善病人治療結果。

結論：根據本院經驗，把放射治療設計改為三維式會增加成本及治療的複雜性，卻未有改善病人的治療結果。對於一些已被證實能改善治療功效的新技術而應用於其設定外時，本研究觀察結果有著重要啟示。

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INTRODUCTION

"[Manufacturers of medical technologies and many physicians] often find expression in rhetoric that conflates *new* with *innovative* and *latest* with *best*."[1] A growing body of evidence suggests that there are many situations in health care where new and more complex technology does not improve outcome compared to simpler, safer, and less expensive alternatives.[2-4] We wondered if we were looking at an example of this situation after completing a project that evaluated outcomes in patients treated in our department with primary radiotherapy for early-stage cervical cancer (stage IB to IIB) over a 25-year period between 1980 and 2005. As we progressed through this project, we noticed that the sophistication of the technology for planning and delivering pelvic radiotherapy had increased substantially during the second half of the study period, without any change in the radiotherapy dose prescription guidelines or in the criteria for selecting patients for radiotherapy at our institution. The main technology change was that in 1996, when we switched from 2-dimensional (2D) treatment planning with conventional radiographs to 3-dimensional (3D) treatment planning with computed tomography (CT) simulation and specialised software. During the years of this study, we did not treat cervix cancer patients with intensity-modulated radiotherapy or image-guided radiotherapy.

This technology was not the only scientific advance during our 25-year study period. The quality of diagnostic imaging improved steadily, new medications for managing treatment complications became available, more attention was paid to completing radiotherapy within 8 weeks,[5] and in the last 5 years most of the treated patients also received cisplatin each week during radiotherapy.[6] We assumed that these factors would improve patient outcomes in the latter half of the study period, but a preliminary analysis suggested that this was not the case. The purpose of this paper was to conduct a detailed analysis of any changes in outcome over time, with a specific focus on our use of more sophisticated technology to plan and deliver radiotherapy in this population of patients, with a high cure rate.

METHODS

All patient information was collected and evaluated for research purposes under the direction of a protocol approved by the University of Florida Institutional Review Board. This study included all 180 patients treated in our department between 1 January 1980 and 31 December 2005. All the patients met the following inclusion criteria: (1) International Federation of Gynecology and Obstetrics (FIGO) stage IB1, IB2, IIA, or IIB carcinoma of the cervix, and (2) treatment with primary radiotherapy with curative intent that involved external-beam radiotherapy to the true pelvis, and staged with computed tomography of the abdomen and pelvis before starting radiotherapy.

All the patients received our standard prescription of primary radiotherapy to the true pelvis followed by 2 brachytherapy implants. We excluded patients from this study if they had histology other than squamous cell carcinoma or adenocarcinoma, a history of supracervical hysterectomy, adjuvant radiotherapy following hysterectomy, hysterectomy immediately after primary radiotherapy, or radiotherapy with brachytherapy alone or brachytherapy with a sidewall boost (no whole-pelvis radiotherapy). Prior to 1 June 1996, pelvic radiotherapy was planned with 2D technology based on orthogonal radiographs taken on a commercial radiotherapy simulator (Ximitron; Varian Medical Systems, Palo Alto, California, US). In early 1996, our department installed a dedicated CT simulator such that after 1 June 1996, all pelvis radiotherapy treatments were planned with CT simulation and 3D planning software (Picker PQ 5000 CT Scanner; Picker International, Cleveland, Ohio and Pinnacle software; ADAC Laboratories, Milpitas, California, US). Table 1 compares the major characteristics of our study populations in our 2 treatment eras.

Treatment

All the study patients received whole-pelvis radiotherapy with the usual dose through the study period being 39.6 Gy at 1.8 Gy per fraction. In both the 2D and 3D era we prescribed the dose at the point of the isocentre. The borders of the anterior and posterior fields for the whole-pelvis treatment were: superiorly at the L4/5 interspace, inferiorly at the middle of the pubic symphisis, and laterally approximately 1.5 cm lateral to the rim of the true pelvis. On the lateral fields of the whole-pelvis treatment, the posterior field border split the rectum in the patients having 2D planning. With 3D planning, the posterior border of the lateral fields was placed 1.5 cm posterior to the cervix. With 2D planning, the anterior border of the lateral field was 1 cm anterior to the pubic symphysis. With 3D planning, the anterior border of the lateral field was either 1 cm anterior to the pubic symphysis or as far anterior as needed to cover the entire uterus. We did not contour normal tissue or target volumes as part of the 3D planning process.

Table 1. Patient and treatment characteristics.

Characteristic	2-Dimensional era (1980-1996), n = 109	3-Dimensional era (1996-2005), n = 71
Variables distributed similarly in the 2 treatment eras		
Stage		
IB1	18 (17%)	9 (13%)
IB2	27 (25%)	19 (27%)
IIA	9 (8%)	5 (7%)
IIB	55 (50%)	38 (54%)
Histology		
Squamous carcinoma	97 (89%)	58 (82%)
Adenocarcinoma	12 (11%)	13 (18%)
Positive pelvic node(s)	22 (20%)	18 (25%)
Elective paraaortic radiotherapy	9 (8%)	5 (7%)
Median whole-pelvis dose (Gy)	40 (39.6 - 67.2)	39.6 (20.0 - 60.0)
% Sidewall boost	47 (43%)	37 (52%)
Mean total dose to point A (Gy)	83	85
Variables distributed differently in the 2 treatment eras		
Concurrent chemotherapy	1 (1%)	28 (39%)
Treatment ≤56 days	40 (37%)	45 (63%)
Cobalt-60 external beam	34 (31%)	0 (0%)
18-20 MV external beam	69 (63%)	70 (99%)
High-dose rate brachytherapy	1 (1%)	12 (17%)

Sidewall boosts of 6 to 10 Gy at 2 Gy per fraction prescribed to the midplane were given through opposed anterior and posterior fields — bilaterally in 40% of the patients and unilaterally in 10% (at the discretion of the treating physician). There was no significant difference in frequency of unilateral and bilateral boosting in the 2D and 3D groups. The borders of the sidewall boost fields were the bottom of the sacroiliac joint superiorly, the superior edge of the pubis inferiorly, 2.5 cm lateral to the midline medially, and 1 cm lateral to the true pelvis laterally.

Elective treatment with radiotherapy to the paraaortic nodes was used in selected patients with large primary tumours or multiple positive nodes on CT scan. To identify patients who received elective irradiation of the paraaortic nodes, we reviewed the port films of all patients with stage IIB disease or positive pelvic nodes at diagnosis. If the superior extent of the field was above the L3/L4 interspace, we coded the patient as having received elective paraaortic-node radiotherapy. Radiographically positive paraaortic adenopathy at diagnosis was treated in the primary field and then boosted with field reductions to approximately 60 Gy.

Brachytherapy doses were difficult to summarise, because the study period spanned the change of low-dose-rate (LDR) intracavitary reporting from mg-radium-hours to the Manchester point of reference system. In this study, we converted mg-radium-hours to a point A dose using a conversion factor derived by Cunningham et al.[7] We started our high-dose-rate (HDR) brachytherapy programme during the last 5 years of the study period. In the small percentage of patients who were treated with HDR brachytherapy, doses were specified as LDR equivalents.[8]

The instructions and devices related to patient positioning, immobilisation, reproducibility, and instructions related to bladder fullness were the same in all study patients. We positioned patients supine with their arms on their upper chest, a wedge-shaped cushion under their knees, and a band around their feet. We did not use a custom body mold and we did not give the patients specific instructions about bladder fullness during simulation or treatment.

Statistical Analysis

Recurrences in the cervix, parametria, vagina, pelvic sidewalls, or pelvic lymph nodes were coded as pelvic failures. Treatment complications were graded using Version 3.0 of the Common Terminology Criteria.[9] For this study, we report only grade 3 to 5 complications because grade 1 and 2 complications were not recorded accurately in our medical record.

All statistical analyses were accomplished with SAS and JMP software (SAS Institute, Cary, NC, US). We used the Kaplan-Meier product limit method to estimate freedom from selected endpoints.[10] The only event in the relapse-free survival calculation was tumour recurrence. The only event in the pelvic control calculation was tumour recurrence in the pelvis. For patients with multiple recurrences, the time to event

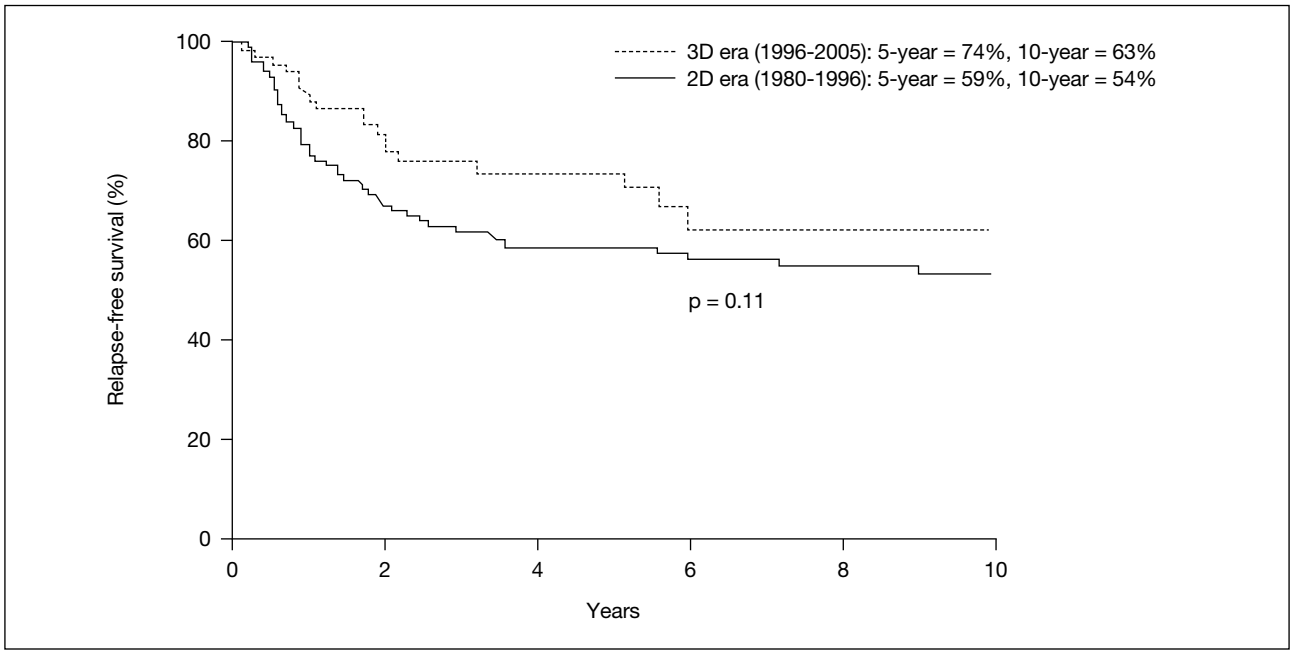

Figure. Relapse-free survival by treatment era.

Table 2. (a) Univariate analysis and (b) multivariate analysis of relapse-free survival.

(a) Variable	Univariate p value	Variable with better outcome
2D vs. 3D planning	0.1067	No significant difference
Stage (IB1/IIA vs. IB2/IIB)	0.0728	No significant difference
Histology (squamous cell vs. adenocarcinoma)	<0.0001	Squamous
Treatment duration (≤56 vs. >56 days)	0.0016	≤56 days
Maximum axial size (≤4 vs. >4 cm)	0.3427	No significant difference
Positive pelvic or paraaortic nodes	0.4646	No significant difference
Concurrent chemotherapy	0.3887	No significant difference
Dose to point A (≤85 vs. >85 Gy)	0.3598	No significant difference

(b) Variable	Multivariate p value	Variable with better outcome	Hazard ratio	95% confidence interval for hazard ratio
2D vs. 3D planning	0.0852	No significant difference	1.7	0.9 - 3.0
Stage (IB1/IIA vs. IB2/IIB)	0.0248	IB1/IIA	2.2	1.1 - 4.4
Histology (squamous cell vs. adenocarcinoma)	<0.0001	Squamous	3.2	1.8 - 5.5
Treatment duration (≤56 vs. >56 days)	0.0041	≤56 days	0.5	0.3 - 0.8
Positive pelvic or paraaortic nodes	0.5832	No significant difference	0.9	0.4 - 1.5
Concurrent chemotherapy	0.8892	No significant difference	0.9	0.4 - 2.4

was set at the first recurrence. The log-rank test statistic was used to detect statistically significant differences in endpoints between strata of selected prognostic factors. We performed a multivariate analysis of relapse-free survival and pelvic control with Cox regression involving a backward selection procedure to create the most parsimonious final model.[11] In both univariate and multivariate analyses, we considered a p value of less than 0.05 to be statistically significant.

RESULTS

The median follow-up time was 3.5 years (range, 0.1-26.0 years) for all patients in our series, 3.9 years (range, 0.1-26.0 years) for patients treated during the 2D planning era, and 3.0 years (range, 0.2-10.6 years) for those treated in the 3D planning era. Patients lost to follow-up were censored at their last follow-up visit.

Sixty-six (37%) patients developed recurrent cervix cancer. The Figure is an actuarial plot of relapse-free survival by treatment era and Tables 2a and 2b summarise the respective results of the univariate and multivariate analyses of variables that might influence relapse-free survival. The differences between patients treated with 2D versus 3D planning were not statistically significant for any comparison.

Table 3. Pattern of tumour recurrence by treatment era.

	2-Dimensional era (1980-1996), n = 109	3-Dimensional era (1996-2005), n = 71	Total
Patients with a recurrence	47/109 (43%)	19/71 (27%)	66/180 (37%)
Site of recurrence (% of all recurrences)*			
Pelvis (all subsites)†	30/47 (64%)	7/19 (37%)	37/66 (56%)
Central	14/47 (30%)	2/19 (11%)	16/66 (24%)
Pelvic node	7/47 (15%)	4/19 (21%)	11/66 (17%)
Subsite unknown	9/47 (19%)	1/19 (5%)	10/66 (15%)
Paraaortic nodes	7/47 (15%)	4/19 (21%)	11/66 (17%)
Distant metastasis	10/47 (21%)	8/19 (42%)	18/66 (27%)

* There was only one site of recurrence per patient with recurrence and the hierarchy of site of recurrence assignment was as follows: Pelvis > Paraaortic nodes > Distant metastasis; and within pelvis: Central > Pelvic node.
† Three patients listed in this table as having pelvic recurrences recurred simultaneously in both the pelvis and paraaortic nodes. The remaining 34 patients had disease limited to the pelvis at the time the recurrent tumour was diagnosed.

Table 4. Complications related to treatment.*

	2-Dimensional era (1980-1996), n = 109	3-Dimensional era (1996-2005), n = 71	Total
Grade 3	1 small bowel obstruction 1 uterine obstruction	2 pulmonary emboli (both had LDR implants)	4
Grade 4	1 utero-sigmoid fistula 1 small bowel necrosis 1 radiation enteritis	1 entero-vaginal fistula 2 small bowel necrosis 3 recto-vaginal fistula 1 abdominal abscess	10
Total	5/109 (5%)†	9/71 (13%)†	14/180 (8%)

* Patients with multiple complications are shown only once and labelled with the most severe complication. There were no fatal (grade 5) complications. Three of the 7 patients with grade 4 complications in the 3-dimensional era received chemotherapy.
† p = 0.3.

Table 3 shows the pattern of relapse by planning era. Pelvic recurrence was more common in the 2D group, but the difference between 2D and 3D was not statistically significant in the multivariate analysis with pelvic control as the endpoint.

Table 4 summarises the patients who developed moderate or severe complications from therapy. The overall complication rate was 8%, and there were no fatal complications. The complication rate was higher in patients treated in the 3D planning era, which may be due to the use of concomitant chemotherapy.

DISCUSSION

The major finding of this study was that more sophisticated technology used to plan pelvic radiotherapy did not improve outcomes in our patients with early-stage cervix cancer to a degree that reached the usual standards for statistical significance. The better relapse-free survival attained with 3D planning (Figure) was what we expected given that these patients were treated in an era when treatment quality had improved for multiple other reasons (i.e., quality of diagnostic imaging, shorter overall treatment times, and concomitant chemotherapy). A higher complication rate in the 3D treatment era also supports our conclusion that this technology did not improve overall clinical outcomes meaningfully.

There is no ideal way to measure the additional time and energy that our patients, staff, and faculty spent as a result of the change from 2D to 3D planning, but it was considerable. The only clear metric that we can describe is the difference in resource utilisation per patient associated with procedures carried out in the 2 treatment eras. Table 5 shows what we charged for each of the subunits of the 2D and 3D planning procedure for pelvic radiotherapy for cervix cancer at our institution in 2009. Total charges for 3D planning were 63% higher than those for 2D planning in this setting.

Studies that Compare 2-Dimensional and 3-Dimensiona Planning for Primary Radiotherapy for Cervix Cancer

Multiple publications extol the potential advantage of using 3D technology to plan pelvic radiotherapy for cervix cancer.[12,13] The authors of these studies conclude that 3D planning should improve patient outcomes because it decreases the chance of underdosage of the posterior aspect of the primary tumour and metastatic pelvic lymph nodes. The limitation of these studies is

Table 5. Per patient charges for 2-dimensional (2D) and 3-dimensional (3D) simulation and planning at our institution in 2009.

	CPT* code	Professional charge (US$)	Technical charge (US$)	Total charges (US$)
2D simulation and planning				
Simulation (complex)	77290	439	1605	2044
Isodose Plan (complex)	77315	439	725	1164
				Total: 3208†
3D simulation and planning				
CT simulation (image acquisition)	77014	-	750	750
Simulation (3D reconstruction)	77295	1281	3195	4476
				Total: 5226†

* CPT denotes current procedural terminology.
† Difference between 2D and 3D total charges: US$2018 = 63% increase.

Table 6. Literature review of tumour control by treatment era.

Institution	Stage	Pelvic failure (%)	Relapse-free survival (%)
2-Dimensional era at the University of Florida (1980-1996)			
Perez et al, Washington University,[14] 1959 - 1979	IB	7	85
	IIA	14	70
	IIB	14	68
Kim et al, Joint Center for Radiation Therapy,[15] 1980 - 1992	IB - IIB	30	70
Keys et al, GOG 71/RTOG 8412,[16] 1984-1991	IB (>4 cm)	26	61
Galloway et al, present study, 1980 - 1996	IB1 - IIB	33	67
3-Dimensional era at the University of Florida (1996-2005)			
Petereit et al, University of Wisconsin,[17] 1989 - 1996	IB	15	85
	II	20	69
Chen et al, Shin Kong Memorial, Taiwan,[18] 1992 - 1997	IB/IIA	4	90
	IIB	10	75
Galloway et al, present study, 1996 - 2005	IB1 - IIB	20	72

that they were dosimetric exercises rather than clinical studies of patient outcome. Ours is the only study that evaluates the major clinical question: Are more cervix cancer patients cured, or are serious complications less frequent, when a specific department changes from using 2D to 3D technology to plan pelvic radiotherapy? In our study of patients treated over the 25-year period ending in 2005, the answer to this question was "No".

Limitations and Explanations of Our Results

Our analysis was limited by all of the factors that compromise the persuasiveness of results from a retrospective study. To crosscheck the integrity of our results, we looked for other studies that reported pelvic control and relapse-free survival in the 2 treatment eras. To date, no single institution has published their results with primary radiotherapy for stage I-II cervix cancer in a single paper or in sequential papers in a way that allows comparison of experience in the 2 treatment eras. The best comparisons we could assess entailed results from different institutions treating patients during the same time period as ours. Table 6[14-18] summarises such information. Given the limitations of this kind of comparison, we interpret these summary findings as showing that our results are similar to those from others.

Another limitation of our study was that mild complications (grades 1 and 2 in the standardised toxicity classification systems) were not evaluated. It is possible that 3D planning decreased mild toxicity rate in our patients, but the retrospective nature of our study meant that we were not able to ascertain such a difference. We interpreted our results in the context of this limitation and realise that our conclusions only apply to the major outcome endpoints like tumour control and moderate and severe complications.

Given the above limitations, what are the possible explanations for why we did not observe a benefit from 3D planning in our study?

One explanation for our findings was that our results are accurate and predictive — meaning that in many communities no meaningful benefit ensues from 3D rather than 2D treatment planning for the external-beam portion of the therapy, in patients treated with primary radiotherapy for early-stage cervix cancer. Those who predicted an important benefit from 3D planning in this

setting ignored 2 factors. First, many practitioners draw 2D fields so that they cover the posterior extent of most cervix cancers. Second, pelvic radiotherapy for cervix cancer is a situation in which minor changes in external-beam dosimetry are unlikely to affect major outcome endpoints.

The papers that concluded that 3D planning should improve cervix cancer cure rates were largely based on data suggesting that 2D planning often results in fields that are too tight on the primary tumour posteriorly. While this may be true in some practices, the philosophy with stage IIB or large-volume IB cervix tumours at our institution has been to place the posterior border of the lateral pelvic fields at the anterior edge of the sacrum or even posterior to the sacrum. We doubt that our 2D fields underdosed the posterior aspect of the high-risk target volume and guess that there are many other practices where posterior coverage is adequate with 2D planning.

Thus, the main reason for planning external-beam radiotherapy for early-stage cervix cancer with 3D technology was unlikely to make an important difference in patient outcome in this situation where the delivered dose with 3D planning was unlikely to cause complications. Moreover, the chance of tumour control was largely determined by other components of the patient's treatment. In primary radiotherapy of cervix cancer, the external-beam dose is usually less than 50 Gy and a major component of the treatment is given with brachytherapy. Historically, the chance of moderate or severe complications from 40 to 50 Gy of conventionally fractionated radiotherapy to the pelvis was very low, such that it would be difficult to demonstrate an important decrease in toxicity from switching to 3D technology. Similarly, the use of brachytherapy makes it unlikely that minor changes in external-beam dose distribution translates into measurable improvements in tumour control. To our knowledge, there is no study where 3D planning improves a major outcome endpoint in a situation where the dose from external beam radiotherapy is no more than 50 Gy.

The 2-Dimensional Versus 3-Dimensional Question in Other Tumour Sites

A comprehensive review of every study related to the 2D versus 3D treatment planning is beyond the scope of this paper. Our summary of the topic is that, in every major tumour site, most studies suggest that 3D planning improves some aspect of patient outcome. Yet in many sites there was at least one study that showed no meaningful benefit. For example in breast and prostate cancers, recently published studies demonstrated no improvement from 3D planning, based on standard endpoints in specific patient subgroups[19] or when outcome was defined by specialised evaluation of organ function.[20]

Implications of Our Findings

One implication of our study was that 3D planning for the external-beam portion of the treatment in patients with early-stage cervix cancer was not necessary. A logical extension of our findings is that 3D planning is of little additional benefit in many other situations involving conventional radiotherapy with total doses in the range of 50 Gy. Recent studies from India, Russia, and Poland are devoted to the question of the value of 3D planning in breast and gynaecological cancers.[19,21,22] Publications like these suggest that the findings in our study will be important to a wide range of oncologists outside the United States.

A broader implication of our study relates to the basic use of new and more complex technology in situations where meaningful improvement in clinical outcomes has not been clearly demonstrated. There is now a large body of evidence that the overuse of inappropriate complex technology in medicine is decreasing the quality and affordability of health care.[2] An excellent summary of the evidence and issues related to this topic are addressed in a recent book by Shannon Brownlee titled *Overtreated: why too much medicine is making us sicker and poorer,*[4] and in a recent commentary titled "Gizmo Idolatry" appearing in the *Journal of the American Medical Association*.[23] Our study is one of the few to look at this question using the major clinical oncology endpoints, and our results suggest that we should be more critical in evaluating new technologies, especially in relation to decisions about major capital equipment purchases. As Emanuel and colleagues remind us, "let us not conflate *new* with *innovative* and *latest* with *best*."[1]

CONCLUSION

New technologies that result in minor changes in the external-beam dose distribution are unlikely to result in a meaningful improvement in the outcomes of patients with early-stage cervix cancer. In radiation oncology departments where resource utilisation is an important issue, planning external-beam therapy with 2D technology is a reasonable option in settings like early-stage cervix cancer, where the target volume is in the pelvis

and the external-beam dose is not more than 50 Gy.

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