Apparent Improvement in Survival for Carcinoma of the Cervix Following the Introduction of Chemoradiation - A Will Rogers Phenomenon

Abstract:
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Abstract
The improved survival for bulky cervical cancers (≥4cm) reported with combination platinum based chemoradiation (1999) prompted a move away from surgery as these cases frequently received adjuvant radiotherapy and were exposed to the morbidity of major surgery. The period pre-1999 (Group 1) was compared with post-1999 (Group 2) when chemoradiation was the preferred treatment for bulky operable cervical cancer. Significantly more cases were treated surgically in Group 1 (79% vs. 62%; P=0.001). Switching from surgery to chemoradiation improved survival in both treatment categories (73% vs. 78% and 37% vs. 44%, respectively) with no improvement in overall survival (70.5% vs. 70.0%). Survival (86%) was similar in both groups among surgically treated women with <4 cm, but significantly more in Group 2 with negative nodes received postoperative adjuvant chemotherapy (Groups 1 vs. 2; 16% vs. 37.5%; P=0.001) and overall the surgically treated patients received more not less multimodality treatment (46.5% vs. 59%; P=0.7).

Introduction
The introduction of combined radiation and chemotherapy has resulted in a new emphasis in the use of this approach in the primary treatment of cervical cancer. This follows three influential publications in 1999 suggesting that the addition of platinum based chemotherapy to radiotherapy dramatically improved survival for locally advanced cervical cancer when compared with standard radiotherapy (1) high risk disease treated with pelvic and para-aortic radiotherapy bulky ≥4 cm cervical cancer combined with adjuvant hysterectomy and, as a result, chemotherapy and radiation was recommended for bulky cervical cancer as an alternative to surgery, as optimum treatment seeks to avoid surgery combined with radiation to minimize treatment-related morbidity. Surgery had been the mainstay of treatment because bulky cancers respond poorly to primary radiation. Such tumors have a high incidence of positive nodes or close tumour margins and receive postoperative adjuvant radiotherapy. Significantly less women received adjuvant chemoradiotherapy, although there was no improvement when comparing primary surgery with radiotherapy in overall or disease-free survival for early stage (<2A) cervical cancer.

At the same time magnetic resonance imaging (MRI) became available and cases previously considered operable were now deemed unsuitable because of early parametrical invasion and/ or suspicious pelvic nodes. As a result, practice changed considerably in that almost all patients with bulky cervical cancers and/ or MRI evidence of nodal involvement or parametrial invasion were treated with chemoradiation. Paradoxically, the resurgence of primary surgical treatment in the early eighties was in response to the fall of the mean age of presentation of cervical cancer from 45 to 35 years, aiming to avoid radiotherapy and thereby conserve ovarian and sexual function in younger women. Rogers phoeni who died of stomach cancer moved to California they raised the average intelligence level in both States and we were particularly interested to see if this applied to our results, as treatment moved from surgery to radiotherapy in a centre where there has been no major change in surgical management during the past 30 years.

Methods
Patients treated before the introduction of chemoradiation in 1999 are designated as Group 1 and after 1999 as Group 2. Cases divided into those with microscopic carcinoma diagnosed following investigation of abnormal cervical cytology and/ or cervical biopsy. The latter were staged (FIGO) following examination under general anaesthetic. This included a vaginal and rectal examination, cystoscopy, documenting the stage and size of the tumor and a cervical biopsy. In the second period of the study (post 1999) there was a tendency to rely on MRI to decide suitability for surgery although the initial staging was clinical. Because of the possibility of stage migration due to the use of MRI, outcome among women with Stage 1B, 2A and 2B in Group 2 treated with primary chemoradiation are considered individually and combined for calculation of survival. All surgery was performed by one of three gynaecologic surgeons. Surgery consisted of a standard radical hysterectomy (parametrium resection to level 2) and pelvic lymphadenectomy (to the level of the common iliac nodes) with conservation of functioning ovaries. All patients with positive nodes and patients with positive or close margins received adjuvant external radiotherapy, combined with chemoradiation in Group 2.

Following publication of GOG 497 suggesting that adjuvant postoperative radiotherapy improved survival in women with risk factors; >1/3 stromal invasion, capillary lymphatic space involvement and clinically large tumour diameter, the indications for adjuvant radiotherapy consisted of a combination of external radiotherapy and brachytherapy and from 1999 this was combined with cisplatinum. No women received para-aortic radiotherapy.

The microstages, 1A and 1B occult are included in the overall survival figures but are not included in the analysis of surgically treated cases as none had positive nodes, received adjuvant radiotherapy or died from disease. Survival among potential surgical cases Stage 1B and 2A, was analyzed by tumor size (> and ≤4 cm). A relatively small number of patients in Stage 3 and 4, with a similar distribution in both groups were included.

Results
Overall 652 women were treated for cervical cancer in the study period; Group 1, pre-chemoradiation, n=386, (1982-1999) and Group 2, chemoradiation, n=263, (1999-2008). There were no differences in the pathological details or distribution by stage of disease (Table 1). There were, respectively, 247 and 131 potential surgical cases (Stage 1B, 2A) having excluded microscopic cases and stages 2B, 3 and 4 (although 12 stage 2B had surgery in Group 1). There was a significant reduction in the number of cases treated surgically (232 of 247; 93.6% vs.102 of 131; 77.8%; P=0.001) which was due to a reduction in surgical treatment of tumour sizes >4 cm (93/97; 95.8% vs.13/33;39%; p=0.001) while the frequency of surgery for tumours ≤4 cm remained the same in both groups (92.6% vs. 89%).

The incidence of positive pelvic nodes in the surgically treated was similar (77/232; 33% vs. 31/102; 30.3%)

The incidence of positive pelvic nodes in the surgically treated was similar (77/232; 33% vs. 31/102; 30.3%) (Table 2). More in Group 2 received adjuvant chemoradiation following surgery but the differences were not significant (115/232; 49.5% vs.62/102; 60.7%;P=0.7) however significantly more women received adjuvant radiotherapy with a tumor size ≤4 cm in Group 2 (18/112; 16% vs.24/64;37.5%; P=0.01) (Table 2) but no significant differences were present among women with <4 cm tumors were over-represented among this cohort but the differences was not significant (29/112;26% vs. 23/64;35.8%; P=0.25). In Group 1 there were no significant differences between the two periods. (273/386; 70.7% vs 185/263; 70.3% and when microscopic cases are excluded (63.8% vs. 61.9%). Survival was similar in both groups treated surgically for <4 cm tumors among those with positive nodes (81% vs. 83.3%) and those with negative nodes (93.6% vs. 89%) (Table 2) Survival was worse in Group 2 for tumors <4cm but the numbers are small (57/93; 61.3% vs. 5/13;38.5%; P=0.056).

All node positive women received adjuvant radiotherapy or adjuvant chemoradiation respectively and while the survival outcome was better in Group 2 the differences were not significant (44/77; 57%;vs.24/34; 70.5%, P=0.6).

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Survival

Survival overall for Stages 1B,2A and 2B treated with radiotherapy improved with chemoradiation for all stages, individually, as well as all stages combined although none of the differences were significant. (Table 3) Survival for surgically treated Group 1 > 4cm (57/93; 61.3%) was similar to chemoradiation in Group 2 > 4cm (11/20; 55%). There were no exenterative procedures in Group 1, compared with 3 in Group 2. Some cases were found to be inoperable and were treated with radiotherapy or chemoradiation. In Group 1, this accounted for 5% (15 cases) of whom 7 died compared with 2.3% in Group 2 (6 cases) all of whom died.

Discussion

The publication of the NEJM papers in 1999 produced a dramatic change in the management of cervical cancer. The first effect was a marked improvement in survival figures among women treated with primary chemoradiation, bringing the results into line with recent published results from the UK. The poor results with radiotherapy in Group 1 were almost certainly due to pre-selection of the best cases for surgery. There were no exenterative procedures prior to 1999 and three were carried out following the introduction of chemoradiation. This is an important consideration because, while the number of treatment failures should be less with combined chemoradiation, as more women are treated with primary radiotherapy, more will come into consideration for an exenterative procedure. The initial switch from surgery to radiotherapy was slow and a number of women with disease > 4cm were treated surgically with poor results (6 of 13 such cases died). However if these cases are excluded from the analysis the improved outcome for surgical cases did not reach statistical significance. These patients cases might not have done well either with chemoradiation.

Women with clinical tumors less than 4 cm and negative nodes have a 5 year survival of 94% and 85% respectively, however almost twice as many of the Group 2 cohort (16% vs.37.5%) received adjuvant chemoradiation; this may in part be explained by a higher incidence of poorly differentiated tumours among the node negative cohort in Group 2. Overall more, not less women are therefore receiving multimodality treatment in the form of adjuvant radiotherapy since chemoradiation was introduced (Group 2 vs 1; 59% vs.49.6%) despite a similar incidence of positive nodes (33% vs.30.3%). One of the main arguments for switching to chemoradiation was the avoidance of combined surgery and radiation, but more women are now being exposed to the potential hazards of this combination. The latter development may be a result of the of the multidisciplinary team approach where it would appear that everyone feels a need to contribute with no one designated to take responsibility for overall management.

Avoidance of radiotherapy is particularly important among pre-menopausal women. The combination of chemotherapy with adjuvant as opposed to primary radiotherapy seems to have been extrapolated following the success with primary treatment. While it is a reasonable therapeutic option, it is without any scientific basis and the results from this study suggests that is adds nothing to survival while significantly increasing cost, side effects and inconvenience for the women. There was a higher incidence of large tumours (> 4cm) in Group 1 which may reflect changes in the staging technique although the incidence of positive nodes (54%) in both groups, if taken as a surrogate marker, suggests not. Hopefully, women are presenting earlier in recent years because of increased awareness of symptoms. The strength of this paper is that all patients presenting to the hospital with cervical cancer are included while presenting results of for one treatment modality e.g. radiation alone is open to selection bias. A negative aspect of the study is the high number of cases lost to follow up particularly among radiation treated cases but the distribution was similar over the two periods. In terms of costs, all cases have an MRI as part of primary staging. Radiotherapy cases have two MRI scans: a primary and a follow up MRI. Adjuvant radiotherapy is used as often as before and chemoradiation is now an addition to primary and adjuvant radiotherapy. Treatment was probably twice or three times as costly overall for Group 2.

In conclusion, overall survival is unchanged despite improved outcomes for both radiotherapy and surgery. Surgery produces excellent results for smaller tumors and the increasing use of adjuvant chemoradiotherapy in this group can be justified and the important test case for the addition of chemotherapy. At first appraisal it seems that tumors > 4 cm should never have surgery but in fact the results suggest that the outcome is no better with chemoradiation except that about 75% of the surgical cohort will receive dual therapy. However, the number of exenterations performed must also be taken into account. The overall conclusion has to be that moving 20% of surgical cases to treatment with radiotherapy improved survival in both groups while the overall survival remained the same-a classic Will Rogers phenomenon.

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References

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