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Original Article

Evaluating the use of external beam radiation alone in the management of cervix cancer

Thuraya Al-Hajri[1], Naghmeh Isfahanian[1], Najlaa Alyamani[1], Soha Atallah[1], E. Choan[1], Tien Le[2], Rajiv Samant[1]

[1]*Division of Radiation Oncology,* [2]*Division of Gynecology Oncology, The Ottawa Hospital, Ottawa, ON, Canada*

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Abstract

Aim: To determine the outcome of patients with locally advanced cervix cancer treated with curative intent using external beam radiotherapy (EBRT), without brachytherapy.

Materials and methods: A chart review was performed of all patients with cervix cancer who received EBRT alone at our centre from 2000 to 2010. Overall survival and local control were evaluated using Kaplan–Meier survival curves.

Results: In total, 22 patients were identified. The median age and follow-up were 56 years and 65 months, respectively. The stage included IB to IVB. Main histology was squamous cell carcinoma (82%). Median tumour size was 5·5 cm. Majority treated with 3D conformal techniques and nine patients (41%) were treated with intensity-modulated radiation therapy (IMRT); 14 patients received doses of ≥65 Gy. Most patients (73%) received weekly concurrent cis-platinum. The major reason for not receiving brachytherapy was locally extensive tumour (59%). The 5-year relapse-free survival and overall survival rates were 57 and 50%, respectively. Seven patients (32%) had a component of loco-regional failure, mainly within the cervix. There was a better outcome among the nine patients treated with IMRT to a median dose of 66 Gy with a loco-regional control of 78%.

Conclusions: Patients who cannot have brachytherapy may still achieve acceptable rates of loco-regional disease control if high radiation doses (>65 Gy) was delivered.

Keywords: brachytherapy; cervix cancer; IMRT; outcomes; radiotherapy

INTRODUCTION

Cervix cancer remains one of the most serious malignancies among women worldwide.[1–3] It is the second most common cancer in women and the third in terms of cancer mortality.[3,4] The gold standard for treating patients with locally advanced stages of cervical cancer is with concurrent radiation and chemotherapy.[4–11] The curative potential of radiation therapy in the management of carcinoma of the cervix is greatly enhanced by the use of intra-cavitary brachytherapy (ICBT).[4,12–14] The American Brachytherapy Society (ABS) recommends that brachytherapy must be included

Correspondence to: Thuraiya Al-Hajri, Division of Radiation Oncology, The Ottawa Hospital, 501 Smyth Road, Ottawa, ON, Canada, K1H 8L6. Tel: +1 613 798 5555, Ext. 70241. Fax: +1 613 247 3511. E-mail: x_thuraya_x@hotmail.com

as a component of the definitive radiation therapy for cervical carcinoma, based on the Patterns of Care studies that show that recurrences as well as complications are decreased when brachytherapy is used in addition to external beam radiation (EBRT).[12,15,16]

However, not all patients are able to receive ICBT due to reasons like extensive local tumour extension, previous subtotal hysterectomy, patient unfit for anaesthesia due to comorbidities, patient refusal and failed attempt at brachytherapy. There is little published literature to evaluate the use and effectiveness of external beam radiation alone with chemotherapy. Therefore, we decided to review our experience among this group of patients. Specifically, with the emergence of more precise and accurate radiotherapy techniques such as intensity-modulated radiation therapy (IMRT), we wanted to evaluate the local control and overall survival outcomes among the small proportion of cervix cancer patients treated radically without brachytherapy. Historically with traditional radiotherapy approaches, EBRT is not as good as brachytherapy in terms of outcomes, both local control and survival. However, there is a limited data about whether outcomes can be improved with more modern approaches using IMRT, concurrent boosts and concurrent chemotherapy. We wanted to see if outcomes were improved with our current modern approaches when brachytherapy was not feasible.

MATERIALS AND METHODS

A retrospective ethics approved single institute study was carried out, and we reviewed patients with locally advanced cancer who were treated at our institution from 2000 until 2010 inclusive with curative intent with EBRT alone.

The patients were staged clinically and all had the following investigations: chest X-ray; computed tomography scan of the abdomen and pelvis; and blood work (including complete blood count, electrolytes, creatinine and magnesium levels). Magnetic resonance imaging scans were often ordered to assess local extent of disease since most patients did not have an examination under anaesthesia, but cystoscopy and sigmoidoscopy were not routinely performed unless clinically indicated. Patient demographics, tumour characteristics, treatment and outcomes were analysed. Overall survival, relapse-free survival and local control were calculated using Kaplan–Meier methods.

All patients were treated at The Ottawa Hospital cancer centre with fairly standard EBRT techniques that have been reported previously.[4] Radiotherapy consisted of using megavoltage radiation (usually 18 MV photons) to treat the whole pelvis to a median dose of 45 Gy in 25 fractions over 5 weeks, using daily 1·8 Gy fractions. EBRT boosts were delivered either sequentially or concurrently in order to deliver a total median dose of 65 Gy (range 45–71 Gy) to the primary site. Nine patients were treated with IMRT approaches, using a Tomotherapy® unit (Accuray Incorporated, Sunnyvale, California, USA) and all of them had concurrent boosts. Of all patients, only one patient received <50 Gy and 14 patients were treated with total doses ≥65 Gy. The median total dose of radiation delivered was 66 Gy with IMRT approaches compared with 57 Gy with non-IMRT approaches.

The reasons for not using brachytherapy were as follows: extensive local tumour extension and inadequate response to initial pelvic radiation (59%), previous subtotal hysterectomy or anatomy inadequate for ICBT (14%), patient unfit for anaesthesia due to comorbidities (14%), patient refusal (9%) and failed attempt at brachytherapy (5%).

The majority of patients (73%) received chemotherapy. It generally consisted of weekly concurrent cis-platinum at a dose of 40 mg/m^2 during pelvic radiation. The median number of cycles delivered was 6. Weekly blood work was carried out to monitor white blood cell and differential counts as well as haemoglobin, electrolyte, creatinine and magnesium levels. The reason for not using chemotherapy among six patients was age ≥75 years.

RESULTS

There were a total of 22 patients identified (see Table 1) that underwent radical radiotherapy with curative intent using EBRT without

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Table 1. *Patient/tumour/treatment characteristics*

Characteristic	Absolute number (%) (n = 22)
Median age (years) (range)	56 (33–90)
Histology subtype	
Squamous cell carcinoma	18 (82%)
Large cell carcinoma	1 (5%)
Adenocarcinoma	1 (5%)
Adenosquamous carcinoma	1 (5%)
Neuroendocrine cancer	1 (5%)
Reason for not receiving brachytherapy	
Local extent of disease	13 (59%)
Age/comorbidities	3 (13%)
Previous hysterectomy	2 (9%)
Patient refusal	2 (9%)
Inadequate anatomy	1 (5%)
Attempt failure	1 (5%)
Stage	
IB	3 (14%)
IIA/B	3 (14%)
IIIA/B	6 (27%)
IVA/B	10 (45%)
Radiation technique	
Non-IMRT	13 (59%)
IMRT	9 (41%)
Treatment modality	
Radiation alone	6 (27%)
Chemotherapy and non-IMRT	7 (32%)
Concurrent chemotherapy and IMRT	9 (41%)

Abbreviation: IMRT, intensity-modulated radiation therapy.

brachytherapy. The median age at diagnosis was 56 years (range 33–90). The most common histology was squamous cell carcinoma (82%). Other histology's include large cell carcinoma (5%), adenocarcinoma (5%), adenosquamous carcinoma (5%) and neuroendocrine cancer (5%). The stage distribution was as follows: stage IB three patients (14%), stage IIA/B three patients (14%), stage IIIA/B six patients (27%) and stage IVA/B ten patients (45%). The median tumour size was 5·5 cm.

With a median follow-up among survivors of 65 months, the relapse-free survival and overall survival rates are 57 and 50%, respectively (Figures 1 and 2). There were a total of ten relapses (45%), and seven (32%) had a component of local failure. Six (27%) had only loco-regional relapses. There were no documented recurrences in 12 patients. The distant failure sites included para-aortic lymph nodes as well as liver, lung and peritoneum, and bones. Most (80%) recurrences

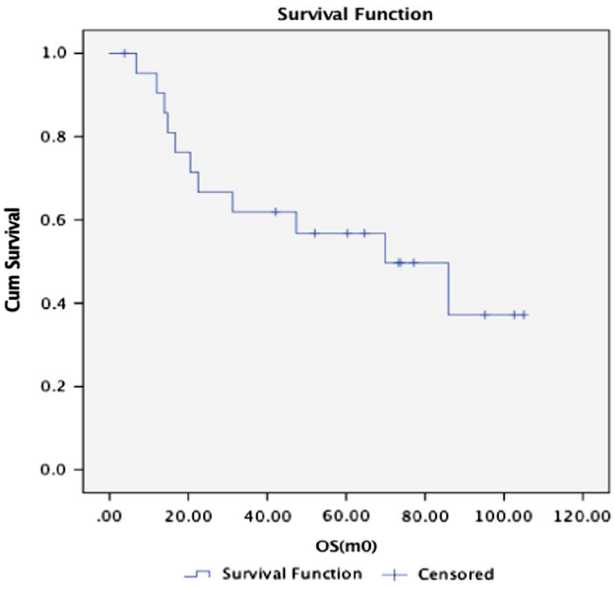

Figure 1. Overall survival.

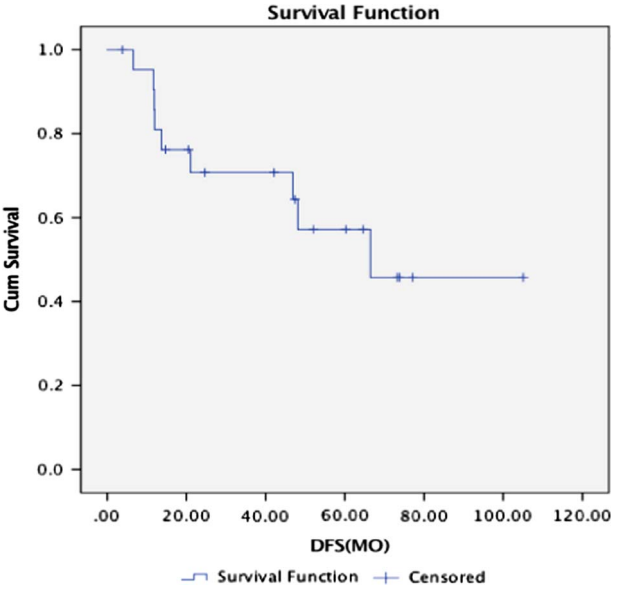

Figure 2. Disease free survival.

occurred within 3 years of initial diagnosis. As shown in Table 2, among the nine patients who were treated with IMRT approaches and concurrent cis-platinum chemotherapy, there were three recurrences (33%), two of which had a component of local failure. The loco-regional control rate for these patients at 5 years was 78%.

Toxicity was difficult to accurately quantify retrospectively but only one patient was not able to complete their radiotherapy as prescribed.

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Table 2. *Patients received chemoradiotherapy with intensity-modulated radiation therapy (IMRT)*

Stage	Maximum tumour size (cm)	Total dose (Gy)	Radiation technique	Treatment	Failure
IIIB	4·5	65	IMRT	ChemoRT	Distant (lung)
IVB	6·3	66	IMRT	ChemoRT	No
IIB	5·1	70	IMRT	ChemoRT	No
IIIB	10·4	64	IMRT	ChemoRT	Local/regional (cervix, iliac lymph node) and distant (liver, lung)
IVA	3·6	70	IMRT	ChemoRT	Local/regional (cervical stump and pelvic/para-aortic lymph nodes)
IIIB	7·3	66	IMRT	ChemoRT	No
IVA	6·6	66	IMRT	ChemoRT	No
IIIA	6·0	66	IMRT	ChemoRT	No
IVA	5·5	65	IMRT	ChemoRT	No

This was due to significant desquamation within the perineum after 50 Gy so the final 10 Gy was not delivered. Approximately 35% of patients had at least mild to moderate diarrhoea acutely. One-quarter of patients who received chemotherapy had significant haematologic toxicity and did not complete the planned minimum 5 cycles as a consequence. In terms of late toxicity, two patients developed vesicovaginal fistulae but they both initially had clinical stage IVA disease with bladder involvement. Two other patients complained of chronic abdominal pain, and a significant vaginal scarring was noted.

DISCUSSION

The combination of EBRT and ICBT is considered to be the standard treatment approach for treating locally advanced carcinoma of the uterine cervix. ICBT has the advantage of delivering a very high dose to the central tumour and a lower doses to the surrounding normal structures, such as the bladder and rectum, resulting in high local control while minimising normal tissue damage.[17] Dose modelling studies unequivocally show that brachytherapy achieves the best radiation dose conformity, tumour dose escalation, and sparing of adjacent normal tissues when compared with advanced external beam modalities including IMRT and proton therapy.[18,19]

Recent technological advances in image-guided planning and delivery of brachytherapy for cervical cancer report impressive local control rates of 100% for stage IB, 96% for stage IIB and 86% for stage IIIB patients.[17,20–23] There is also emerging evidence suggesting that combining interstitial and ICBT techniques can further improve radiation doses for cervix cancers while limiting doses to adjacent organs at risk. However, it has been recognised that in some clinical situations (such as bulky lesions, narrow vaginal apex, inability to enter the cervical os, lower vaginal involvement and pelvic sidewall disease), traditional ICBT may be suboptimal.[12] Therefore, the ABS recommends the use of interstitial approaches to improve adequate target coverage if necessary.[13,16,24]

Although brachytherapy achieves excellent results, a significant proportion of patients do not receive it, and the reasons for omitting brachytherapy vary.[25] Han et al.[26] reported an analysis of 7,359 patients using the Surveillance, Epidemiology, and End Results (SEER) database who received EBRT for cervical cancer between 1988 and 2009. During the period of the study, there was a 25% reduction in brachytherapy use and a 13% reduction in the cause specific survival rate. The revision of the SEER coding manual may have partially accounted for a portion of the decline in the brachytherapy use and cancer-specific survival that was observed. Their study nonetheless raises concerns related to the potential for substandard care as a result of omitting brachytherapy when treating locally advanced cervix cancers.[26,27] According to Han et al. SEER review,[26] brachytherapy treatment was associated with higher 4-year cause specific survival (64·3 versus 51·5%, $p < 0{\cdot}001$) and overall survival (58·2 versus 46·2%, $p < 0{\cdot}001$).[26]

Our single institution experience of treating locally advanced cervix cancer with EBRT alone

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confirms suboptimal outcomes. However, among these patients, we were simply unable to use ICBT and tried to compensate as best we could with the technology and equipment available to us. Our findings are similar to those reported recently by a Swedish group.[28] Although we agree that the best outcomes thus far have been achieved with the inclusion of brachytherapy,[4,12] there will always be some patients that are not able to get brachytherapy. These patients were the focus of the current study and we wanted to evaluate their outcomes, and identify ways to potentially improve outcomes. We hope that our findings can provide some guidance to optimise their treatment.

If there are situations where brachytherapy cannot be applied, then the option of adding a boost to higher doses can be done, either concurrently or sequentially, with the goal still being to maximise the loco-regional control. The outcomes in some situations may be more comparable to the standard approach using brachytherapy. We found that reasonably good local control is still possible in situations when external beam doses of 65 Gy or more are used to treat the primary tumour, preferably with modern IMRT approaches, along with concurrent cis-platinum chemotherapy. Grossly involved nodal disease should also be boosted and the literature suggests ≥55 Gy.[29] With image-guidance in conjunction with IMRT now widely available, it should be possible to deliver these doses while safely limiting radiation doses to normal structures.

Despite the small size, our group of patients (nine) treated with IMRT approaches had 78% local control. Only two patients failed locally at the cervix and one of those patients also failed within the pelvic and para-aortic lymph nodes. The patients with local failures had stage IIIB and IVA disease. Severe late toxicity does not appear to be a major issue based on our limited data.

Many single institutions evaluated the use of definitive IMRT with brachytherapy in the treatment of cervix cancer but there is very little published literature on the use of IMRT alone without using brachytherapy for the primary management of cervix cancer.[27] Haas et al.[30] reported on six cervical cancer patients who had anatomic or medical conditions that precluded ICBT. The patients received stereotactic body radiotherapy (SBRT) boost to the cervix instead, using the doses of 20 Gy in five fractions (five patients) and 19·5 Gy in three fractions (one patient). With a median follow-up of 14 months, there were no reported local failures and no toxicities from the SBRT boost. These results are encouraging but more research and longer follow-up is required before this can be considered a viable alternative to brachytherapy.

Our study did not adequately assess toxicity and likely larger studies are needed to address this issue. However, Mundt et al.[31] did a preliminary analysis of chronic gastrointestinal (GI) toxicity in gynaecology patients treated on an adjuvant basis with intensity-modulated whole pelvic radiation therapy (IM-WPRT). The results suggested that IM-WPRT is associated with less chronic GI toxicity than conventional pelvic radiotherapy.

Treating cervix cancer remains challenging but many patients with locally advanced disease can still achieve successful outcomes. Based on decades of published studies and clinical experience, radiotherapy is essential for the management of locally advanced cervix cancer, and brachytherapy should be utilised whenever possible. However, despite importance of brachytherapy, there will likely be some patients who are unable to undergo this procedure. If brachytherapy is not possible, then a radical approach can still be considered with external beam radiation, possibly with an image-guided IMRT approach. If high doses of radiation can be delivered to the primary tumour and grossly involved lymph nodes along with concurrent chemotherapy, then loco-regional disease control is possible in most patients. We suggest treating the primary cervix tumour to ≥65 Gy and the grossly involved lymph nodes to ≥55 Gy along with concurrent 5–6 cycles of chemotherapy. We cannot achieve the results seen with brachytherapy but our data suggests an IMRT approach is an acceptable option and that loco-regional control can be achieved in the majority of patients.

Our study has limitations because of the small number of patients, the heterogeneity of the

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patient population and the variability in the treatment approaches used. However, we hope our findings can help clinicians managing patients with locally advanced cervix cancer in situations where brachytherapy is not possible. Fortunately, this represents a relatively small proportion of all cervix cancer patients, but nonetheless, we need to evaluate for effective treatment options for them. Hopefully, as more centres publish their experience, it will help improve the care for this group of patients.

CONCLUSION

Treating locally advanced cervix cancer with high-dose radiotherapy (≥65 Gy) using modern IMRT approaches along with concurrent chemotherapy shows promise among patients not suitable for brachytherapy, and can potentially lead to good loco-regional control with acceptable levels of toxicity.

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Conflicts of Interest

None.

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