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Editorial

Concurrent chemobrachytherapy in locally advanced cervical carcinoma: A hypothesis worth exploring

Introduction

Globally, carcinoma of uterine cervix is the fourth most common malignancy among women (1). It remains a major health problem in developing countries where most patients (60–80%) present in advanced stages and nearly 50% of them succumb to their disease (2). Therefore, management of the locally advanced carcinoma cervix (LACC) continues to be a challenge. External beam radiotherapy (EBRT) with concurrent chemotherapy followed by brachytherapy is the standard treatment for LACC worldwide after the landmark National Cancer Institute alert in 1999 (3). Although survival improved by about 10% with the use of concurrent chemoradiotherapy (CCRT), the benefit may be less in Stages IIB–IVA. Patients of these stages were underrepresented in the five landmark National Cancer Institute trials which lead to the establishment of CCRT. Subsequently, the results of a meta-analysis revealed survival advantage of only 3% in advanced stage (III–IVA) patients (4). Attempts to increase survival in this subset of patients by including neoadjuvant/adjuvant chemotherapy or intensification of existing CCRT protocols are ongoing in clinical research protocols. One of the factors associated with dismal survival outcomes in these patients is presence of clinical residual disease in as high as 30% of patients at the end of EBRT (5). The 5-year overall survival in patients with residual disease was found to be 33.7% vs. 62.6% ($p = 0.0001$) in patients with no residual disease in a study by Saibishkumar *et al.* (5). Although not considered standard as of now, concurrent integration of radiosensitizers or chemotherapy drugs having radiosensitizing effect during brachytherapy treatment seems to be rational and a potentially effective regimen in these patients. The issue of concurrent chemobrachytherapy (CCBT) for all cancers in general remains unclear due to paucity of literature. We aimed to review the existing literature regarding the use of CCBT in the management of LACC and discuss the concerning issues.

Skepticism about CCBT

CCBT is presently not practiced in the radiotherapeutic treatment of LACC mainly due to the skepticism of increased toxicity (6, 7). The American Brachytherapy Society (ABS) guidelines (7) published in year 2012 clearly state "Although no data support an increase in toxicity, given the large fraction sizes used with HDR, the ABS recommends that chemotherapy not be administered on a brachytherapy day but rather on an EBRT day, given the potential for increased complications because of normal-tissue sensitization." The concerns thus are more theoretical rather than based on evidence. The current ABS recommendations (7) might have been possibly influenced by previous ABS guidelines (6) which recommended not to use CCBT due to high complication rates reported by three trials (8–10). However, scrutiny of these three trials reveals that high complication rates were not precisely due to CCBT. First, all these trials were conducted and reported from a single center. Second, radiotherapy consisted of EBRT (46 Gy) plus three high-dose-rate (HDR) intracavitary brachytherapy treatments given weekly (30 Gy to Point A), concurrent with the last 3 weeks of EBRT. Thus, the scheduled overall treatment time was relatively shorter (4.5 weeks), and in the last 3 weeks, a cumulative dose of 60 Gy to Point A was delivered. Third, relatively higher HDR dose per fraction (10 Gy) was used in all these trials. Fourth, the authors have not mentioned whether chemotherapy was given on the day of brachytherapy, and therefore, it is difficult to interpret if the high complication rates were because of CCBT. Finally, all three trials were nonrandomized studies with small sample sizes (less than 50 patients).

Another trial which could have exerted a negative influence on authors who framed current ABS guidelines (7) is the study by Gaspar *et al.* (11) showing increased toxicity with CCBT in esophageal carcinoma. Twelve percent patients in this study (11) developed fistula; however, the radiation dose used in this study was relatively higher (50 Gy EBRT followed by 15 Gy in three fractions of HDR brachytherapy) than the dose prescribed in commonly practiced regimes. Results of this study should not be extrapolated to cervical carcinoma because esophagus is a serial organ and has markedly different radiation tolerance as compared with cervix.

Rationale for using CCBT

There are several biological rationales which encourage us to investigate the role of CCBT in cervical carcinoma:

1. **Benefit of radiosensitization with chemotherapy**: Randomized controlled trials in cervical cancer treatment

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have established that concurrent chemotherapy given with EBRT improves local control and overall survival (3). Chemotherapy administered concurrently with brachytherapy may play a similar role and provide incremental benefit over brachytherapy alone. More than 40% of dose is delivered by brachytherapy, and this remains a good opportunity to enhance the effect of brachytherapy by integrating chemotherapy particularly in patients with residual disease. Yahya Abadi *et al.* (12) in a Monte Carlo evaluation of enhancement of brachytherapy doses with cisplatin found out that the dose enhancement factor (ratio of the dose in a voxel within tumor when the chemotherapy agent exists in the tumor, to the dose at the same voxel in an agent-free tumor) with a 5% concentration of cisplatin was 1.25 for ^{192}Ir (the most commonly used HDR brachytherapy source) and 4.13 for ^{125}I. This study justifies the biological rationale, although more preclinical and clinical work needs to be done in this regard to accurately quantify the enhancement of brachytherapy doses with CCBT.

2. **Maximizing the benefits of the 4Rs of radiobiology**: The 4Rs of radiobiology are repair, reoxygenation, repopulation, and reassortment. Both sublethal damage repair (repair between fractions) and potentially sublethal damage repair (repair due to manipulations of postradiation environment) occur *in vitro* in cervix cancer cell lines. Many studies have demonstrated that hypoxic cervix tumors are more refractory to radiotherapy (13, 14). Concurrent chemotherapy and RT result in more rapid tumor response. Similarly, CCBT may decrease the hypoxic fraction by decreasing cancer volume between brachytherapy fractions. Squamous cell cancers such as head and neck cancer and cervix cancer are sensitive to repopulation. Fyles *et al.* (15) and others have documented an approximate 1% loss of local control when treatment is prolonged greater than 30 days. CCBT likely accelerates loss of clonogens, making repopulation less likely. Finally, CCBT may permit reassortment: shifting cancer cells into a more radiosensitive phase (G2M). Common chemotherapeutics used in cervix cancer such as taxanes are known to exploit this mechanism (16). In addition to the well-known 4 Rs, more recent data have demonstrated that chemotherapy and radiation together may enhance the therapeutic window by exploiting the genetic instability of tumors, greater sensitization in a low pH microenvironment, and increased cell kill in specific pathways such as epidermal growth factor receptor mutations (17).

3. **Reduced toxicities with image-based brachytherapy**: Brachytherapy in carcinoma of the cervix has shifted from Point A–based prescription to image-guided optimized plans with consequent reduction in doses to nearby organs at risk (3). Considering the sharp dose fall off, limited volume of irradiation, and adequate coverage of the residual disease with image-guided brachytherapy planning, CCBT is less likely to increase the complication rates. In fact, a prospective trial has documented reduction in toxicities with image-guided brachytherapy compared with centers where that was not practiced (18).

4. **Potential benefit in patients having residual disease after EBRT**: Patients with gross residual disease at the end of EBRT have a dismal outcome. Concurrent chemotherapy and radiotherapy result in greater local control and more rapid tumor response. This heightened response may permit more organ sparing in the image-guided era.

Evidence supporting feasibility of CCBT in LACC

The results of various published trials are briefly summarized in Table 1. Although most studies in the literature are Phase I/II or retrospective studies, but the results suggest that CCBT is feasible in LACC.

Table 1
Studies in the literature on concurrent chemobrachytherapy in locally advanced cervical carcinoma

Authors [reference]	Dose rate of brachytherapy	Number of patients of LACC	Response rates/ survival outcomes	Toxicities
Koumantakis *et al.* (19)	LDR	36	CR 33%; LC 90%	- No Grade III/IV acute or late toxicities - Grade II late bowel or bladder toxicity: 20%
Kuske *et al.* (20)	LDR	15	52% disease free at last followup	- Grade II/III acute toxicity: 18% and 22%, respectively - Grade II/III late sequel: 17.3%
Aghili *et al.* (21)	MDR	40	LC 93.5%	- No acute Grade III/IV toxicity - Grade II/III late cystitis: 22% and 3% - Grade II/III late proctitis: 3%
Vrdoljak *et al.* (22)	LDR	62	4-year OS 88.7%	- Grade III/IV late toxicity: 16%
Giridhar *et al.* (23)	HDR	10; 14 (no chemotherapy with brachytherapy)	CR 100%; CR 90%	- Grade III/IV hematological toxicity in both arms: 0 pt - Grade IV gastrointestinal toxicity with CCBT: 1 pt
Petric Mise *et al.* (24)	LDR	118	LC 97.5%; 8-year OS 75%	- Grade III–IV late local toxicity: 18.8%
Eifel *et al.* (25)	LDR	195; 195 (no chemotherapy)	8-year OS 67%; 8-year OS 41%	- Grade III–IV late local toxicity in both arms: 14%

LACC = locally advanced cervical carcinoma; LDR = low dose rate; CR = complete response; LC = local control; MDR = medium dose rate; OS = overall survival; HDR = high dose rate; CCBT = concurrent chemobrachytherapy.