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Locally Advanced Carcinoma of the Uterine Cervix: Current Issues in Developing Countries and Future Research

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Abstract

Locally advanced carcinoma of the uterine cervix is a major public health problem in developing countries. In spite of advancement in chemoradiation therapy, the outcome of locally advanced disease remains suboptimal. Newer diagnostic methods, treatment approaches and technology to evaluate the response needs to be evaluated in this condition. Some of the current issues of management of cervix cancer in developing countries are discussed in this present review. The direction of future research in imaging and neoadjuvant therapy are highlighted.

Keywords: Carcinoma of uterine cervix; Chemoradiation; Neoadjuvant therapy

Introduction

Carcinoma of the uterine cervix is one of the most common cancers in developing countries like India. More than 80% patients present in a fairly advanced stage [1]. According to the GLOBOCAN statistics, the estimated incidence of cervical cancer in the world is 528000 per year with 266000 annual deaths attributed to cervical cancer (approximately 50%) [2]. India alone contributes to 23% of the total global cases annually. With an annual 67000 deaths, cervical cancer remains one of the major causes of cancer related mortality in India [3]. The staging system proposed by International Federation of Obstetrics and Gynecology (FIGO) is widely followed and correlate well with prognosis [4]. Briefly stage I consists of disease confined to the cervix (IA: microscopic and IB: clinically demonstrable lesion). Stage II disease extends beyond the cervix but not involving pelvic side wall or lower third of vagina.

Involvement of these later structures including hydronephrosis or non-functioning kidney is classified as stage III disease. Stage IV disease extends well beyond the pelvis or involves the mucosa of the bladder or rectum [4]. FIGO system can be followed even in resource constrained situation and is a robust system for predicting survival even though it does not take into account other prognostic factors like endometrial extension, stromal invasion, lympho-vascular extension or radiological nodal involvement [5]. Radiotherapy is the mainstay of treatment for locally advanced cancer of the cervix (stage IIB to IVA). Radiotherapy consists of combination of external beam radiotherapy and brachytherapy to deliver adequate tumoricidal dose to the gross and microscopic tumor [6]. In conventional radiotherapy, target volume encompasses the true pelvis including the primary tumor, pelvic and lower para-aortic nodes. External beam radiotherapy is followed by brachytherapy to boost the primary tumor. In brachytherapy, a very high dose can be delivered to a small volume sparing the normal organs.

Radiotherapy in carcinoma of the cervix

Various retrospective series have shown that 40-50% disease control rate can be achieved at 5 years for locally advanced carcinoma cervix with radiotherapy alone. [1]. Montana et al., reported disease free survival at 5 year for IB, IIA, IIB, IIIA and IIIB as 83%, 76%, 62%, 26% and 35% respectively [7] . Retrospective outcome analysis from India, reported disease free survival of 56% and 40% at 8 years for stage IIB and IIIB respectively with radical radiotherapy. [1]. In a more recent study Azad et al., reported a 3 year disease free survival of 80%, 70%, 40% and 11% for stage I, II, III and IV cervical cancer respectively by radiotherapy alone [6]. Therefore, for locally advanced cervical cancer, treatment outcome with radiation therapy is suboptimal. Till the beginning of this century radiotherapy alone was the standard of care. Pattern of care study in United States showed that almost 70% of locally advanced cervical cancer patients were treated with radical radiotherapy between 1996-1999 [8].

Concurrent chemoradiation in carcinoma of the cervix

In 1999, results of several large randomized trials of concurrent chemotherapy with radiation changed the standard of care for advanced carcinoma cervix. Whereas, the studies involving neoadjuvant chemotherapy followed by radiotherapy, failed to show desired benefit, there was significant reduction in risk of recurrence with concurrent chemoradiotherapy. Pattern of care study, showed the change of practice of management of locally advanced cervical cancer after 1999, with as many as 63% patients receiving chemoradiation [8]. Addition of chemotherapy with radiation increased the locoregional disease control and survival. Various regimens of chemotherapy were tried during this period which can be classified into platinum based (cisplatin alone or in combination) and non-platinum based. Several trials have successfully investigated the role of addition of chemotherapy to radiotherapy [9-13].This was followed by National Cancer Institute alert urging clinicians to use chemoradiation for cervical cancer [14]. Majority of the studies showed survival benefit, which was further confirmed by Cochrane meta-analysis [15]. The meta-analysis results showed that the addition of chemotherapy to radiotherapy leads to a 12% increase in overall survival [15]. An

updated meta-analysis reducing the heterogeneity of the earlier analysis compared data from 13 trials which compared chemo radiotherapy with same radiotherapy. The 5 year survival benefit with chemoradiation was 6% (hazard ratio 0.81, p<0.001) [16]. There was a suggestion that magnitude of the survival benefit was more for earlier stage disease [16]. Even though chemoradiation became the standard of care, the evidence of benefit of chemotherapy for advanced stage disease was not so strong and overall survival for such advanced, bulky disease still remains suboptimal.

Chemoradiation in locally advanced carcinoma cervix in developing countries

Chemoradiation markedly increased the hematological and gastrointestinal toxicity and overall complexity of the treatment [8]. Higher incidence of acute toxicities, poor nutritional status of patients makes it difficult to implement it in developing countries. Moreover, it remained uncertain whether patients with locally advanced disease actually benefit from chemo-radiotherapy [17]. Few Indian studies have evaluated the role of chemoradiation in locally advanced cervical cancer. Negi et al. conducted a prospective randomized study of chemoradiation vs. radiation alone of 102 patients with stages IIA-IVA cervical cancer. This study did not show any benefit of concurrent chemoradiation compared to radiation alone [18]. In another randomized trial, reported by Mitra et al. no statistically significant increase in overall or disease free survival was reported with chemo radiotherapy [19]. Another large randomized trial from India, reported by Srivastava et al. also did not show a survival benefit with concurrent chemoradiotherapy compared to radiation alone (58% vs 60%) in a group of 305 patients with stage Ib-IVa cervical cancer [20]. In fact, the role of chemoradiotherapy in locally advanced cervical cancer especially in the context of developing countries has been questioned keeping the risk of combination regimen and overall benefit [17]. This paradoxical effect observed in advanced tumors in developing countries has been attributed to the increased acute toxicity resulting in more frequent treatment breaks with resultant increase in overall treatment time, accelerated repopulation [17]. In developing counties like India, particularly due to prevailing socio-economic conditions, it is very difficult to administer the optimum five cycles of concurrent chemotherapy as recommended by earlier GOG protocol [21]. Therefore, newer treatment modalities, in addition to the present standard of care of concurrent chemoradiotherapy, need to be explored for better tumor control in locally advanced disease.

Role of neoadjuvant chemotherapy

One of the approaches adopted was to add neoadjuvant chemotherapy prior to the loco-regional treatment. Neoadjuvant chemotherapy effectively reduces the tumor size, eliminates micrometastasis and down stage the tumor [22]. However, the significance of these benefits in terms of survival has not been proven conclusively in the literature, especially in locally advanced disease [23]. Interestingly, from the meta-analysis of neoadjuvant chemotherapy in cervical cancer, it was evident that, trials that gave more intensive chemotherapy in terms of a shorter cycle or higher dose intensity, resulted in better overall survival. Therefore, modification of existing neoadjuvant protocols is required to improve the therapeutic outcome. Dose dense chemotherapy is one of the modifications suggested in the literature [24,25]. One of the other approaches is chemopotentiation of chemotherapy with the addition of low dose radiation. Recent radiobiological investigations have shown that ultra-

fractionated low dose of radiotherapy (0.5-1 Gy) can increase the efficacy of cell cycle specific chemotherapy [26-29]. At this dose, radiation leads to arrest of the proliferating cells in G2 phase by inducing DNA repair mechanism. Addition of G2 phase specific chemotherapy can lead to increased cell kill [30]. This phenomenon is called chemopotentiation and it has been shown to be a clinically feasible and effective approach in head and neck cancer, glioblastoma, breast cancer, non-small cell lung cancer, endometrial cancer and pancreatic cancer [31-37]. Combination of low dose radiation with chemotherapy to increase the efficacy is based on radiobiological synergism due to chemopotentiation. Modification of neoadjuvant chemotherapy by dose dense approach or by chemopotentation by low dose radiation has been reported in the literature to improve the therapeutic outcome [24,25,30]. Das et al. reported 84% disease control at 3 years in cervix cancer with ultra-fractionated low dose radiation and chemotherapy followed by chemoradiation [38]. The role of neoadjuvant chemotherapy especially in the context of chemoradiation requires further evaluation.

Advancement in imaging technology

Use of magnetic resonance imaging (MRI) especially functional MRI like diffusion weighted imaging (DWI) has improved the diagnostic and therapeutic efficacy in cervix cancer. MRI enabled image guided adaptive brachytherapy has improved the outcome as shown in various studies [39,40]. Escalation of dose with sparing of the normal structures is possible by this approach which can deliver significantly high dose to the tumor. Diffusion weighted MRI has improved the diagnostic accuracy of malignancies in gynecological cancers. MRI can help to stage the disease more accurately due to better soft tissue delineation especially in the context of parametrial and lower uterine segment involvement. It can also help to differentiate radiation induced tissue changes from residual disease [41-45]. Recently it has been shown that Positron Emission Tomography (PET) scan can improve the diagnostic accuracy especially in case of recurrent and metastatic disease [46], however, the role of PET scan in cervix cancer is still translational.

Conclusion

In conclusion, advanced carcinoma of the uterine cervix continues to be a therapeutic challenge in developing countries. Use of modern radiation therapy technology especially adaptive radiation with image guidance, newer chemotherapy approaches and functional imaging can improve the therapeutic outcome of this condition. In future, the correlation of radiological or imaging markers with pathological prognostic markers should be investigated.

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