International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Bharaswadkar G. Int J Reprod Contracept Obstet Gynecol. 2020 Sep;9(9):3912-3914
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: http://dx.doi.org/10.18203/2320-1770.ijrcog20203884

Review Article

Role of neo-adjuvant chemotherapy followed by surgery in cervical cancer: a review

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Received: 24 June 2020
Accepted: 31 July 2020

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ABSTRACT

Incidence of cervical cancer is predominantly found in developing countries. In Indian set up, it is most commonly found in rural locations in younger population. Chemotherapy was initially introduced for the treatment of recurrent/metastatic cervix cancer and has subsequently been explored in primary treatment either as neo-adjuvant prior to radiation or surgery in an attempt to reduce the incidence of loco-regional recurrence. The review study tries to evaluate the role of neoadjuvant chemotherapy (NACT) followed by surgery in cervical cancer management. Randomized trials and meta-analysis were analysed. Most of them used short course chemotherapy course of 4-6 weeks followed by surgery. patients with high risk pathological features received postoperative RT. The results of trials indicated significant reduction in the risk of death with NACT, but there were few differences between the trials. NACT followed by surgery is found to be associated with an improved response rate and progression-free survival. However, the impact on overall survival remains to be confirmed.

Keywords: Cervical cancer, Neo-adjuvant chemotherapy, Surgery

INTRODUCTION

Cervical cancer is a common malignancy among women in countries with limited resources. In India, its incidence varies from 13-24/100,000 women per year. While cervical cancer continues to be a common malignancy in rural India, it is preceded by breast cancer in urban India.[1] Clinical presentation for cervical cancer in India has features distinct from those seen in industrialized nations: young age at diagnosis (median age 35-38 versus 50-58 years), higher frequency of squamous histology (>90 versus ≤80%) and presence of locally advanced stage (stage IIB-IVA) in >80% of women with a higher disease volume compared to ≤50%.[2] The outcome for early-stage cervical cancer is generally good: the 5-year survival rates for locally advanced disease vary from 50 to 65% for stage IIB, from 28 to 35% for stage IIIB and from 5 to 15% for stage IVA disease. Thus, 30-50% of patients develop treatment failure; loco regional recurrence is the main cause of failure. The presence of a big primary tumor (bigger tumors tend to have hypoxic foci which are relatively radio-resistant) and/or pelvic/para-aortic lymph nodes har boring metastatic disease are possible contributing factors. Chemotherapy was initially introduced for the treatment of recurrent/metastatic cervix cancer and has subsequently been explored in primary treatment either as neo-adjuvant prior to radiation or surgery or as adjuvant after radiation or surgery. Currently, chemotherapy administered concurrently with radiation therapy (concurrent chemo radiation, CCRT) is the standard treatment for locally advanced cervical cancer. Authors have made an attempt to review the role of neo-adjuvant chemotherapy followed by surgery in the management of cervical cancer.

DISCUSSION

In stage II B-IV A, residual disease in almost one third of patients after sequential NACT and RT led investigators to hypothesize that the surgical extirpation of the

remaining tumor mass may be associated with survival benefit. Many phase III studies using NACT followed by surgery with or without adjuvant RT revealed encouraging results.[3,4] Later this issue was addressed in a number of randomized trials (Table 1) and meta-analysis.[5-12]

Table 1: Randomized studies of NACT and surgery in patients with cervical carcinoma.

Authors	Stage	Patients, n	Regimen	Survival		P value
				NACT + Sx (%)	Sx/RT (%)	
Chang et al[5]	IBT-IIA	124	VBP	2-year OS=81	84	N.S.
				5-year OS=70	61	N.S.
Benedetti Panici et al[6]	IB2-III	441	Variable	5-year OS=58.9	RT: 44.5 at 5 years	<0.07
				PFS=55.4	41.3	<0.02
Napolitano et al[7]	IB-IIA	NACT-Sx =106	VBP	5-year OS:		
		Sx/RT=86		IB-IIA=78.6	73.2	N.S.
				IIB=68.7	64.3	N.S.
				5-year DFS:		
				IB-IIA=71.1	64.3	<0.05
				IIB=56.2	57.1	N.S.
Eddy[8]	IB bulky	288	VP	IB-IIA:	IB:	
				5-year OS=78 versus 73%	68 versus 64	N.S.
				5-year DFS=77 versus 64	56 versus 57	
				p<0.05	p=N.S.	
Cai et al[9]	IB	CT-Sx=52 versus Sx alone=54		5-year OS=84.6		<0.01
				(CT arm) versus 75.9		
Katsumata et al[10]	IB2, IIA2, IIB	NACT-Sx versus Sx alone	BOMP	5-year OS NACT		
				Arm=70		
				Sx arm=74.4		0.85

Adapted from[15], Sx: surgery, VBP: vincristine, bleomycin and cisplatin, VP: vincristine and cisplatin, BOMP: bleomycin, vincristine, mitomycin-C and cisplatin, OS: overall survival, PFS: progression free survival, DFS: disease free survival.

Chang et al randomized 124 patients of stage I B-II A to receive either 3 cycles of cisplatin, vincristine or bleomycin followed by either hysterectomy (n=68) or primary pelvic RT (n=52).[5] The cumulative survival was 81% versus 84% at 2 years and 70% versus 61% at 5 years in the NACT and RT arms, respectively. There was not remarkable difference in disease free survival between the 2 arms.[5] In a similar study by Benedetti-Panici et al survival advantage with this strategy was limited to stage IB2-IIb.[6] Most of these studies used short course chemotherapy of 4-6 weeks followed by surgery or radiotherapy.[3-9,14] Katsumata et al for the Japan clinical oncology group, have reported results of a phase III trial.[10] Patients with stage IB2, II A2 and II B received 2-4 cycles of the BOMP regimen (bleomycin, vincristine, mitomycin C and cisplatin every 3 weeks) followed by radical surgery versus radical surgery alone. Patients with high risk pathological features received postoperative RT. The 5-year overall survival rate was 70% in the NACT group compared to 74.4% in the radical surgery group (P+0.85). 58% of patients received postoperative RT in the NACT group compared to 80% in the radical surgery group (p<0.01).[10] In a meta-analysis of individual patient data of patients treated with NACT followed by surgery compared with radical RT alone, data from 5 trials and 872 patients was obtained. The combined results from all trials (HR=0.65, 95% CI=0.53-0.80, p=0.0004) indicated a highly significant reduction in the risk of death with NACT, but there were some differences between the trials in their design and results.[13]

In a meta-analysis, Kim et al reviewed data of five randomized trials and four observational studies.[11] In patients with stage IB1-IIA, NACT prior to surgery reduced the need for adjuvant radiation therapy by decreasing tumor size and lymph node metastasis, and distant metastasis but it failed to improve survival compared to patients who underwent primary surgery.[11] Rydzewska et al for the recently cochrane database of systematic reviews, have analyzed the results of six

randomized studies.[12] Both overall survival (HR=0.77, 95% CI 0.62-0.96, p<0.02) and progression -free survival (PFS) were significantly improved with NACT (HR=0.75, 95% CI=0.61-0.93, p=0.008). There was no difference in the effect of NACT with respect to total cisplatin dose, chemotherapy cycle length or cervical cancer stage.[12]

CONCLUSION

NACT administered at a shorter interval (e.g., weekly) prior to radical surgery for patients with early-stage cervical cancer (IB2, IIA) appears to be associated with an improved response rate and progression-free survival. However, the impact on overall survival remains to be confirmed. The present management of cervical cancer requires a multidisciplinary team approach. For patients with early disease, the plan to go for upfront surgery or NACT followed by surgery should be based on systematic review of clinical findings, pathology, imaging and availability of surgical skills which allows the patient to make informed decision about initial treatment modality.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Bharaswadkar G. Role of neo-adjuvant chemotherapy followed by surgery in cervical cancer: a review. Int J Reprod Contracept Obstet Gynecol 2020;9:3912-4.