Asian Pacific Journal of Cancer Care
Vol 7 No 1 (2022), 55-59
Original Research

Patterns of Failure in Node Positive Cervical Cancer Patients Treated with Radical Radiotherapy

Geetha Muttath	Department of Radiation Oncology, Malabar Cancer Centre, Thalassery, Kerala, India.
Greeshma Keloth Erakkotan	Department of Radiation Oncology, Malabar Cancer Centre, Thalassery, Kerala, India. 2 Radiographer, Government Medical College, Manjeri,India
Vinin Narayanan	Department of Radiation Oncology, Malabar Cancer Centre, Thalassery, Kerala, India
Joneetha Jones	Department of Radiation Oncology, Malabar Cancer Centre, Thalassery, Kerala, India.
Arun. P. Narendran	Department of Radiation Oncology, Malabar Cancer Centre, Thalassery, Kerala, India
Nabeel Yahiya	Department of Radiation Oncology, Malabar Cancer Centre, Thalassery, Kerala, India
Akhil. P. Suresh	Department of Radiation Oncology, Malabar Cancer Centre, Thalassery, Kerala, India
Muhammed Minhaj	Radiographer, Government Medical College, Manjeri,India.
Muhammed Riyas	Division of Clinical Research and Biostatistics, India.

Background: Chemoradiation plays an important role in cervical cancer treatment but dose to organs at risk (OAR) is the limitation while escalating dose to target. With conformal techniques dose escalation is made possible without increase in toxicities. Though node positive cervical cancers have poorer prognosis delivering higher dose to the involved nodes have shown benefit. We aim to determine the patterns of failure in node positive cervical cancer patients treated with chemoradiation and to determine the grade III and IV toxicities associated with it.
Methods and Materials: In this retrospective study node positive cervical cancer patients treated with conformal radiotherapy were analysed. 45 Gy -50.4 Gy was given to the pelvis and 55 Gy to positive nodes with sequential or simultaneous integrated boost (SIB) in 25 -28 fractions with weekly cisplatin 40mg/m2 followed by brachy therapy. Extended fields were used to treat patients with positive para aortic lymph nodes. Treatment toxicities were recorded as per CTCAE version 4.3.
Results: Of the 62 patients 87.1% had squamous cell carcinoma and majority were in stage II (38.7%). At a median follow up of 33 months two (3.2%) patients had local recurrence, eight (12.9 %) had distant failure and one (1.6%) had loco regional recurrence. Lung was the most common site of metastasis followed by the supraclavicular region. The 3 year overall and disease free survival were 91.4 % and 77.2 % respectively. Stage of the disease (p=0.001) and residue at the end of therapy (p-0.010) showed significant association with DFS but not with OS. 21 (33%) had Grade III –IV toxicities, nine (13%) having acute toxicities and 12 (19.4%) had late toxicities.
Conclusion: Though node positive cervical cancers have poor prognosis our study showed that aggressive management improves the outcome without increase in toxicities.

Introduction

Globally cervical cancer is the fourth common cancer and second most common cancer in women

[1]. In India it is the second commonest cancer after breast cancer in women [2]. Though there are awareness programmes and screening programmes majority of these patients still present with locally advanced disease in our part of the world [3, 4]. Incidence of metastasis to pelvic and paraaortic lymph node increases as stage advances [5, 6]. One of the important prognostic factor in cervical carcinoma is lymph nodal metastasis [7]. The presence of pelvic lymph node metastases has been associated with increased pelvic recurrence and distant metastases, and a decrease in overall survival [8-12]. As of now the standard of care for stage IB2 – IVA carcinoma cervix is concurrent chemoradiation [13]. In patients with paraaortic lymph node metastasis, extended field radiotherapy (EFRT) has shown improvement in survival at the expense of increased toxicities [14]. However EFRT delivered with conformal techniques like 3 DCRT and IMRT results in decreased toxicity compared to conventional radiation therapy. With IMRT or VMAT toxicities are lesser than 3DCRT and dose escalation is also possible with these techniques without increasing the incidence of grade III and IV bowel toxicities [15].

In this study we aim to analyse the outcome of node positive cervical cancer patients treated at our centre with protocol treatment using VMAT and to assess the associated grade III/IV toxicities.

The primary objective is to determine the patterns of failure in node positive cervical cancer patients treated with radiotherapy or chemo-radiation. Other objectives are to determine the factors associated with treatment failure, to analyse the disease free survival and overall survival and associated grade III and IV toxicities.

Materials and Methods

This was a retrospective study done at the Department of Radiation Oncology, Malabar Cancer Centre, Kerala. The patients included in the study were cervical cancer patients with positive pelvic and /or paraaortic lymph node who were treated with concurrent chemoradiation or radiotherapy alone from Jan 2015 to Dec 2016.

Patients whose case records do not have documentation on details of treatment or toxicities and those who were not treated with conformal therapy were excluded from the study.

Methodology

All patients diagnosed with cervical cancer underwent planning CT scan adhering to bladder filling protocol. Patients were advised to drink 750 ml of fluid with oral contrast in 30 minutes and wait for 30 more minutes. Bowel was evacuated by giving laxatives given on previous night. Immobilisation was done using vacuum cushion with a custom made leg separator to maintain the position of the lower limb. Contrast enhancing CT scans were done using CT simulator (GE Optima) with 2.5 mm slice thickness. After full bladder sequence another sequence was taken after emptying the bladder. The images were exported to the contouring station. All node positive patients underwent PET CT to rule out metastasis elsewhere. Target volumes and organs at risks were contoured by the radiation oncologist and dosimetrist respectively (MIM 6.8.6). Treatment plans were generated with conformal technique3DCRT/VMAT (MONACO version 5.11). Extended fields were used to treat patients with positive paraaortic lymph nodes. Patients were treated up to a total dose of 45 Gy -50.4 Gy to the pelvis and gross nodes were treated up to a dose of 55 Gy. After plan evaluation and approval plans were transferred to the treatment machine (Varian ClinaciX, Elekta – Versa HD) and treatment was executed. Concurrent chemotherapy was given with weekly CDDP 40 mg/m2. After completion of CTRT, intra cavitary brachytherapy 6-7 Gy in 3-4 fractions were given. At the end of EBRT clinical examination was done for response assessment. oncologists. Radiation toxicities were recorded in the radiation charts as per CTCAE version 4.3. After treatmen, patients were reviewed at one month and thereafter they were followed up once in 3 months upto 3 years and then 6 monthly upto 5 years and yearly after that. Demographic details, comorbidities, local stage of the disease, node involvement, number of nodes, size and site of the

nodes involved, treatment technique, dose and fractionation, chemotherapy, treatment duration, brachytherapy details and toxicities and status at last follow up, site of failure, were collected from the RT charts, case records and Treatment Planning System (TPS). *Statistical Analysis* Descriptive and inferential statistics was used for data analysis. Kaplan Meier method was used for calculating the disease free and overall survival. Reverse Kaplan- Meier method was used to calculate the median follow up period. IBM SPSS Statistics (Version 20.0. Armonk, NY: IBM Corp) was used for analysis. Overall survival (OS) was defined as the time period from the date of chemoradiation to death due to any cause or last follow up. Disease free survival (DFS) was defined as the time period from the date of chemoradiation till the development of recurrence. A p value of <0.05 was significant. Results A total of 62 patients with node positive cervical cancer were included in the study. 26 (42%) patients had comorbidities, of which 8 (31%) had multiple comorbidities. Majority 54 (87.1%) patients were having squamous cell carcinoma, 6 (9.7%) had adenocarcinoma and 2 (3.2%) had adenosquamous carcinoma. The clinical details are given in Table 1. Majority of patients were in stage II (38.8%) followed by stage III (32%), stage IV (21%) and stage I (8.1%) (AJCC7th edition). Of the 62 patients 54 (87%) patients received chemo radiation of which 27 patients (43.5%) completed five cycles of chemotherapy and five patients (8%) received For patients who had gross residue in the parametrium or vagina Interstitial brachytherapy was done. Patients on EBRT were reviewed once in a week by Radiation oncologists. Radiation toxicities were recorded in the radiation charts as per CTCAE version 4.3. After treatmen, patients were reviewed at one month and thereafter they were followed up once in 3 months upto 3 years and then 6 monthly upto 5 years and yearly after that.

Demographic details, comorbidities, local stage of the disease, node involvement, number of nodes, size and site of the nodes involved, treatment technique, dose and fractionation, chemotherapy, treatment duration, brachytherapy details and toxicities and status at last follow up, site of failure, were collected from the RT charts, case records and Treatment Planning System (TPS).

Statistical Analysis

Descriptive and inferential statistics was used for data analysis. Kaplan Meier method was used for calculating the disease free and overall survival. Reverse Kaplan- Meier method was used to calculate the median follow up period. IBM SPSS Statistics (Version 20.0. Armonk, NY: IBM Corp) was used for analysis. Overall survival (OS) was defined as the time period from the date of chemoradiation to death due to any cause or last follow up. Disease free survival (DFS) was defined as the time period from the date of chemoradiation till the development of recurrence. A p value of <0.05 was significant.

Results

A total of 62 patients with node positive cervical cancer were included in the study. 26 (42%) patients had comorbidities, of which 8 (31%) had multiple comorbidities. Majority 54 (87.1%) patients were having squamous cell carcinoma, 6 (9.7%) had adenocarcinoma and 2 (3.2%) had adenosquamous carcinoma.

The clinical details are given in Table 1.

Variables	Types	Number(62)	%
Comorbidities	DM	8	13
	HT	7	11
	CAD	3	5
	MULTIPLE	8	13
	NONE	36	58
Histology	SCC	54	87
	Adenocarcinoma	6	9.6

	Adenosquamous	2	3.2
Stage	I	5	8
	II	24	38.7
	III	20	32.3
	IVA	1	1.6
	IVB	12	19.4
Nodal site	External lilac	53	85.5
	Internal iliac	19	30.6
	Common Iliac	20	32.3
	Para-aortic	13	21
	Presacral	4	6.5
Number of nodes	Single	19	30.6
	Multiple	43	69.4
Bilateral	32 (51.6)		
Multiple sites	39 (62.9)		
Largest node in cms	<=1.5	8	12.9
	>1.6-<2.5	24	38.7
	>/=2.5	30	48.4

Table 1. Clinical Details of Node Positive Cervical Cancer Patients Treated with Radiotherapy at Malabar Cancer Centre.

Majority of patients were in stage II (38.8%) followed by stage III (32%), stage IV (21%) and stage I (8.1%) (AJCC7th edition).

Of the 62 patients 54 (87%) patients received chemo radiation of which 27 patients (43.5%) completed five cycles of chemotherapy and five patients (8%) received weekly carboplatin. 13 patients who had para aortic node were treated with extended field RT with VMAT. 96.8% of patients received planned brachytherapy.

The median treatment duration was 54.5 days (Range: 34-68 days) and it did not show any correlation with disease failure. At completion of EBRT 18 (29 %) patients had residual disease at local site. Treatment details are given in Table 2.

Variables	Types	Number(62)	%
Treatment	RT	8	12.9
	CTRT	54	87.1
Total RT dose	55/50.4/28#	13	20
	55/45/25#	32	51.6
	50.4 /28#	17	27.4
RT portal	Pelvis	49	79
	Extended field RT	13	21
Chemotherapy	No	8	12.9
	Yes	54	87.1
Chemo drug	Cisplatin	49	79
	Carboplatin	5	8.1
No.of cycles	II	4	6.5
	III	1	1.6
	IV	18	29
	V	27	43.5
	VI	4	6.5
Brachytherapy	No	2	3.2
	Yes	60	96.8

Table 2. Treatment Details of Node Positive Cervical Cancer Patients Treated with Definitive Radiation or Chemoradiation in Malabar Cancer Centre.

The median follow up was 33 months. 11 patients had recurrence in which 8 (12.9%) patients had distant failure, 2 (3.2%) patients had local recurrence and 1 (1.6%) had pelvic node.

Loco regional recurrence was seen in one (1.6%) patient. Local recurrence was confirmed by correlating clinical findings pathologically and radiologically. Lung was the most common site of metastasis followed by supraclavicular region. Two-sided Fisher's exact test confirmed that there is a statistically significant association between stage (P=0.001) and residue at completion of EBRT (P=0.010) with recurrence status. Of the four patients died, 3 died due to disease and one patient due to cardiac cause. Patterns of failure are depicted in Figure 1.

Figure 1. The Patterns of Failure in Node Positive Patients Treated with CTRT.

A Kaplan-Meier method was run to determine the disease free survival function. It is observed that out of 62 cases, numbers of recurrent cases were 11 and numbers of censored cases were 51.

Since the number of events is less than 50% of the observations, the median disease free survival time cannot be estimated from a Kaplan Meier curve. The mean disease free survival time is 49 months (95% CI: 45- 53 months).The 3 year overall and disease free survival were 91.4 % and 77.2 % respectively Disease free and overall survival is depicted in Figure 2 and 3.

Figure 2. DFS of Node Positive Cervical Cancer Patients Treated with CTRT.

Figure 3. OS of Node Positive Cervical Cancer Patients Treated with CTRT.

Toxicity Analysis

Of the 62 patients grade III –IV toxicities were seen in 21 (33%). Nine (13%) patients had acute toxicities and 12 (19.4%) had late toxicities. Correlation between dose of RT and RT portal with toxicities was done, but was not statistically significant. The details of toxicities are shown in Table 3.

Grade of Toxicity		Acute (9)			Late (12)	
	Rectum	Bladder	Small Bowel	Rectum	Bladder	Small Bowel
III	0	3	6	9	2	0
IV	0	0	0	0	0	1

Table 3. Toxicities Associated Radiotherapy/ chemo-radiation in Node Positive Cervical Patients.

Most of the patients had acute small bowel toxicities whereas among the late toxicities majority were large bowel toxicities. One patient had small intestinal obstruction.

Discussion

Cervical cancers are the second commonest cancer in India among women. External beam

radiotherapy with concurrent chemotherapy followed by brachytherapy is the standard of care in cervical caners as of now.

In a study by Zhikai Liu analysis of stage IIB cervical cancers showed that 25.8% of patients had positive lymph nodes and majority of the nodes were in externl iliac, internal iliac and obturator nodes and the least number of nodes were in the presacral and common iliac group which is in concordance with our study [16].

In our study at a median follow up of 33 months 11 patients had recurrence. Majority of patients had distant metastasis, lung being the most common site. In a study byAnisBandyopadhyay et al stage at presentation, histology, treatment duration and treatment gap were associated with treatment failure [17]. But in our study stage of the disease and residue at end of therapy were significantly associated with failure. Size or site of the node, lymph nodes at multiple sites or multiple lymph nodes or total dose of RT did not show any association with recurrence as expected. The mean duration of treatment in our cohort of patients was 54 days and 68 % of patients completed treatment within 56 days. Except for two patients who refused brachytherapy none of our patients had break during radiotherapy.

A study on patterns of recurrence in node positive cervical cancer patients was done by Rajni Sethi et al showed that the 3-year overall survival (OS) and disease- free survival (DFS) were 65% and 50% respectively. In our study at median follow up of 33 months, the three year OS and DFS was 91.4% and 77.2% respectively. Regarding the pattern of failure, in their study majority of patients had distant failure similar to the findings in our study [18].

E.M. Osborne et al studied on definitive Extended- Field Radiation Therapy for Cervical Cancer patients with para-aortic lymph node metastases and the rate of grade 3 or higher late toxicities was 17% and most frequently involved the gastrointestinal and genitourinary systems [19-21]. In our study 13% of patients had acute and 19.4% had late toxicities. Majority had small bowel toxicity in the acute phase.

In conclusion, node positive cervical cancer is known to have poor prognosis. The current retrospective analysis shows that with aggressive management, the overall survival and disease free survival could be improved. The recurrence in our study is low compared to other studies. Longer follow is desired for more authentic conclusion. But being a retrospective analysis, inherent flaws of retrospective studies may be attributed to better result. The diagnosis of nodal positivity is based on radiological findings and the pathological involvement is unknown. Hence the possibility of pathologically node negative diseases might have been included in the analysis. Prospective studies with pathological evaluation of nodes and longer follow up may be required to confirm the findings.

References

References

1. International Agency for Research on Cancer. 2018. GLOBOCAN 2018 Database. *Lyon, France: International Agency for Research on Cancer; Available from: http://www.gco.iarc.fr [Last accessed on 2020 Jul 02].*
2. NICPR Cancer Statistics. Available at http://cancerindia.org.in/statistics/ Accessed 11 July 2018.
3. Sharma Aadhya, Kulkarni Vaman, Bhaskaran Unnikrishnan, Singha Meher, Mujtahedi Saad, Chatrath Anshul, Sridhar Mallika, Thapar Rekha, Mithra P. Prasanna, Kumar Nithin, Holla Ramesh, Darshan B. B., Kumar Avinash. Profile of cervical cancer patients attending Tertiary Care Hospitals of Mangalore, Karnataka: A 4 year retrospective study. *Journal of Natural Science, Biology, and Medicine*. 2017; 8(1)DOI

4. Jain Aanchal, Ganesh Balasubramaniam, Bobdey Saurabh C., Sathwara Jignasa A., Saoba Sushma. Sociodemographic and Clinical Profile of Cervical Cancer Patients Visiting in a Tertiary Care Hospital in India. *Indian Journal of Medical and Paediatric Oncology: Official Journal of Indian Society of Medical & Paediatric Oncology.* 2017; 38(3)DOI
5. FengfengXie, Lihua Gong, Xiuxiu Chen, Xiujie Zhu, Lizhi Liang. Distribution of pelvic lymph nodes as well as preoperative and surgical pathologic factors associated with nodal metastases in women with cervical cancer. *Int J ClinExpPathol.* 2017; 10(4):4801-4806.
6. Tsunoda Audrey Tieko, Marnitz Simone, Soares Nunes Joao, Mattos de Cunha Andrade Carlos Eduardo, Scapulatempo Neto Christovam, Blohmer Jens-Uwe, Herrmann Jörg, Kerr Ligia Maria, Martus Peter, Schneider Achim, Favero Giovanni, Köhler Christhardt. Incidence of Histologically Proven Pelvic and Para-Aortic Lymph Node Metastases and Rate of Upstaging in Patients with Locally Advanced Cervical Cancer: Results of a Prospective Randomized Trial. *Oncology.* 2017; 92(4)DOI
7. Benedetti-Panici P., Maneschi F., Scambia G., Greggi S., Cutillo G., D'Andrea G., Rabitti C., Coronetta F., Capelli A., Mancuso S.. Lymphatic spread of cervical cancer: an anatomical and pathological study based on 225 radical hysterectomies with systematic pelvic and aortic lymphadenectomy. *Gynecologic Oncology.* 1996; 62(1)DOI
8. NCCN clinical practice guidelines in oncology. Cervical cancer. Version2. 2013. *http://www.tri-kobe.org/nccn/guidelinegynecological/english/cervical.pdf. Accessed in April 27, 2015.*
9. Fleming Nicole D., Frumovitz Michael, Schmeler Kathleen M., Reis Ricardo, Munsell Mark F., Eifel Patricia J., Soliman Pamela T., Nick Alpa M., Westin Shannon N., Ramirez Pedro T.. Significance of lymph node ratio in defining risk category in node-positive early stage cervical cancer. *Gynecologic Oncology.* 2015; 136(1)DOI
10. Lee Hyun Jin, Han Seungbong, Kim Young Seok, Nam Joo-Hyun, Kim Hak Jae, Kim Jae Weon, Park Won, Kim Byoung-Gie, Kim Jin Hee, Cha Soon Do, Kim Juree, Lee Ki-Heon, Yoon Mee Sun, Kim Seok Mo, Kim Ji-Yoon, Yoon Won Sup, Lee Nak Woo, Choi Jin Hwa, Park Sang-Yoon, Kim Joo-Young. Individualized prediction of overall survival after postoperative radiation therapy in patients with early-stage cervical cancer: a Korean Radiation Oncology Group study (KROG 13-03). *International Journal of Radiation Oncology, Biology, Physics.* 2013; 87(4)DOI
11. Je Hyoung Uk, Han Seungbong, Kim Young Seok, Nam Joo Hyun, Kim Hak Jae, Kim Jae Weon, Park Won, Bae Duk Soo, Kim Jin Hee, Shin So Jin, Kim Juree, Lee Ki Heon, Yoon Mee Sun, Kim Seok Mo, Kim Ji Yoon, Yoon Won Sup, Lee Nak Woo, Choi Jin Hwa, Park Sang Yoon, Kim Joo Young. A nomogram predicting the risks of distant metastasis following postoperative radiotherapy for uterine cervical carcinoma: A Korean radiation oncology group study (KROG 12-08). *Radiotherapy and Oncology.* 2014; 111(3)DOI
12. Voordeckers Mia, Vinh-Hung Vincent, Van de Steene Jan, Lamote Jan, Storme Guy. The lymph node ratio as prognostic factor in node-positive breast cancer. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology.* 2004; 70(3)DOI
13. FIGO Committee on Gynecologic Oncology. FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics.* 2014; 125(2)DOI
14. Polterauer S., Hefler L., Seebacher V., Rahhal J., Tempfer C., Horvat R., Reinthaller A., Grimm C.. The impact of lymph node density on survival of cervical cancer patients. *British Journal of Cancer.* 2010; 103(5)DOI
15. Cozzi Luca, Dinshaw Ketayun Ardeshir, Shrivastava Shyam Kishore, Mahantshetty Umesh, Engineer Reena, Deshpande Deepak Dattatray, Jamema S. V., Vanetti Eugenio, Clivio Alessandro, Nicolini Giorgia, Fogliata Antonella. A treatment planning study comparing volumetric arc modulation with RapidArc and fixed field IMRT for cervix uteri radiotherapy. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology.* 2008; 89(2)DOI
16. Zhai De-Yin, Yin Yong, Gong Guan-Zhong, Liu Tong-Hai, Chen Jin-Hu, Ma Chang-Sheng, Lu Jie. RapidArc radiotherapy for whole pelvic lymph node in cervical cancer with 6 and 15 MV:

a treatment planning comparison with fixed field IMRT. *Journal of Radiation Research.* 2013; 54(1)DOI

17. Liu Zhikai, Hu Ke, Liu An, Shen Jie, Hou Xiaorong, Lian Xin, Sun Shuai, Yan Junfang, Zhang Fuquan. Patterns of lymph node metastasis in locally advanced cervical cancer. *Medicine.* 2016; 95(39)DOI
18. AnisBandyopadhyay, Upasana Mukherjee, SandipGhosh, SauravGhosh, Shyamal Kumar Sarkar, Loco Regional Failure in Locally Advanced Cervical Cancer, APJCP.2018.19.1.73.
19. RajniSethi, JyotiMayadev, Suresh Sethi, Dominique Rash,, Lee-may. Patterns of Recurrence in Node-Positive CervicalCancer Patients Treated With Contemporary Chemoradiation and Dose Escalation:A Multi-Institutional Study Chen , Practical Radiation Oncology ,2018 xx, e1-e7.
20. E.M. Osborne, A.H. Klopp, A. Jhingran, L. Meyer, P.J. Eifel; MD. Anderson Cancer Center, Houston, TXDefinitive Extended-Field Radiation Therapy for Cervical Cancer Patients With Para-Aortic Lymph Node Metastases. 93(3):S202-S203.
21. Osborne Eleanor M., Klopp Ann H., Jhingran Anuja, Meyer Larissa A., Eifel Patricia J.. Impact of treatment year on survival and adverse effects in patients with cervical cancer and paraortic lymph node metastases treated with definitive extended-field radiation therapy. *Practical Radiation Oncology.* 2017; 7(3)DOI