RESEARCH ARTICLE

CEA as a Tumor Marker in Predicting Pelvic and Para-aortic Lymph Node Metastasis in Squamous Cell Carcinoma Cervix

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Abstract

Background: Carcinoma cervix is the major cause of death from gynecological malignancies. Isolated paraaortic lymph node metastasis detected on the initial diagnosis of cervical cancers could be addressed via extended paraaortic lymph node irradiation. Serum Carcinoembryonic antigen (CEA) is useful in detecting early Para aortic lymph node (PALN). **Materials and Methods:** Fifty patients of histologically proven squamous cell carcinoma of cervix have been recruited into the study. We assessed pelvic and Para aortic lymph node status via CT or MRI scans. Serum CEA ranges had been evaluated in all from stage I to IV before starting the treatment. **Results:** We observed that high pretreatment CEA values were associated with the pelvic and paraaortic lymph node metastasis 65.2% of the patients with high pretreatment CEA value had PALN metastasis (p=0.002). 47.8% of the patients with high CEA had pelvic lymph nodal metastasis (p=0.077) and 70% of the patients with high pretreatment CEA had both Pelvic and PALN metastasis which was statistically significant (p=0.020). **Conclusion:** Carcinoembryonic antigen levels should help to prognosticate the Carcinoma Cervix patients and predict the presence of Para-aortic and Pelvic lymph nodes. This may be effective tool for detecting early failures in patients with Carcinoma Cervix.

Keywords: Tumor Marker- CEA- Cervical cancer- Para-Aortic Lymph node- Pelvic Lymph node

Introduction

Cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women, with an estimated 604,000 new cases and 342,000 deaths worldwide in 2020 [1]. Most common histologic subtype of cervical cancer is squamous cell Carcinoma [2]. Carcinoembryonic antigen (CEA) is a glycoprotein found in colorectal carcinomas [3] that has also been studied in other mucin-producing tissues such as the uterine cervix. Serum CEA was quantified in cervical neoplasms by Rutanen et al. [4] in 1978, who found increased values in 10% of squamous carcinomas. In the literature, overall sensitivity has been described from 39 to 69% and there was an association between percentage of detection and clinical stage of disease, increasing from 26% of cases diagnosed of stage I disease to 71% of stage III disease and 100% of stage IV disease [5-8]. Studies have focused on CEA for over 40 years, suggesting it's a useful tool in describing the prognosis of cancer [9]. A tremendous correlation has been stated between pre-treatment CEA levels and extent of the disease. High pre-treatment values had been related to bad prognosis [10].

Lymph node (LN) metastasis is an independent prognostic factor for cervical cancer patients [11]. The rate of para-aortic lymph node (PALN) metastases was found to be 5-45 per cent in locally advanced cervical cancer (LACC) [12]. PALN positivity primarily depends on pelvic lymph nodal involvement. The other key factors increasing the probability of PALN involvement are tumor size, parametrial and/or uterine corpus involvement [13]. PALN involvement has been proven to be a detrimental factor in the overall survival of cervical cancer patients irrespective of primary tumor size [14].

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The 2018 FIGO (International Federation of Obstetrics and Gynecology) staging system has incorporated lymph nodal involvement; hence, the importance of accurate lymph nodal assessment is compounded and has direct implications on the mode of management [15].

For patients at suspicion of Para-aortic and Pelvic lymph node involvement imaging for metastatic workup is recommended. Extended Pelvic lymph node dissection ought to be taken into consideration accompanied by extended field external beam radiation therapy (EBRT) for patients with para-aortic lymph nodes [16]. Lymphadenopathy can't be judged clinically, and it requires radiological investigations like CT scan, MRI scan and PET-CT scan.

CEA is a reliable tumor marker in patients with carcinoma of the cervix.[17] The presence of lymph node metastases has extra stated impact on the CEA values than the primary tumor.[18] There has been a lack evidence in the literature comparing pretreatment CEA values and its correlation with lymph node metastasis. Hence this study was conducted to correlate the pretreatment CEA values and presence of lymph node metastasis in Carcinoma Cervix.

Materials and Methods

50 patients of biopsy proven carcinoma cervix of any age were prospectively recruited into the study after taking approval from the institutional ethical committee. A written informed consent has been obtained from all the patients. They were clinically staged using FIGO staging system. In the evaluation of Para-aortic and pelvic lymph node involvement, CT scan or MRI scan was performed in all patients. The criterions for positive node involvement were based on the axial diameter of the lymph node larger than 1 cm. Patients with distant metastasis were excluded from the study. Pretreatment Serum CEA levels were evaluated in all the patients.

Statistical Methods

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean, Standard Deviation (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, 1. Dependent variables should be normally distributed, 2. Samples drawn from the population should be random, and Cases of the samples should be independent. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Leven`s test for homogeneity of variance has been performed to assess the homogeneity of variance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, non-parametric setting for Qualitative data analysis.

Results

The total of 50 patients of carcinoma cervix were included in the study. Age of patients ranged between 21-70 years with the mean age of 51 years. Most of the patients in the study were aged between 40 -60 years and majority of them were in advanced stages i.e. IIB, IIIB, IVB.

Para-aortic lymph node was detected with CT scan or MRI scan in 42 % of patients and 50 % of patients there was pelvic lymph node involvement. In a total of 50 patients, 21 patients were Paraaortic node positive, 25 patients were pelvic node positive, 10 patients were both pelvic and paraaortic node positive. CEA value < 3 ng/ml

Table 1. Comparison of Para aortic Lymph Node According to CEA levels of Patients Studied (p=0.002).

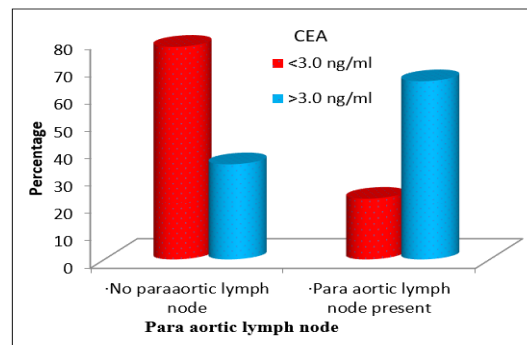| PALN	CEA ng/ml)		Total
	<3.0 (n=27)	>3.0 (n=23)	(n=50)
Present	6 (22.2%)	15 (65.2%)	21 (42%)
Absent	21 (77.8%)	8 (34.8%)	29 (58%)

Figure 1. Comparison of Para aortic Lymph Node According to CEA levels of Patients Studied (p=0.002).

Table 2. Comparison of Pelvic Lymph Node According to CEA levels of Patients Studied (p=0.777)

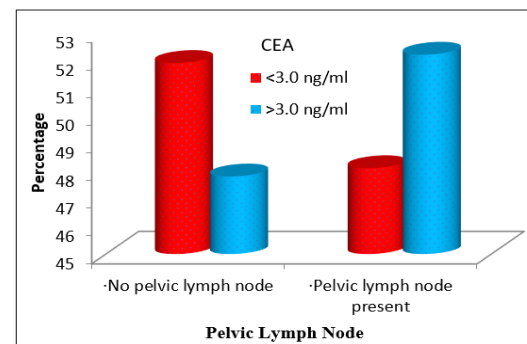| Pelvic Lymph Node	CEA (ng/ml)		Total
	<3.0 (n=27)	>3.0 (n=23)	(n=50)
Absent	14 (51.9%)	11 (47.8%)	25(50%)
Present	13 (48.1%)	12 (52.2%)	25(50%)

Figure 2. Comparison of Pelvic Lymph Node According to CEA levels of Patients Studied (p=0.777)

Table 3. Comparison of CEA Levels when both Pelvic and Para Aortic Nodes are Present (p-0.020)

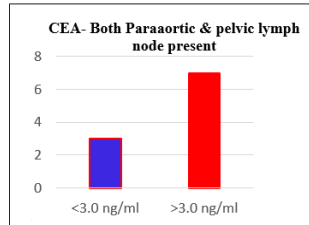| CEA (ng/ml)	Para-aortic & pelvic lymph node present (p-0.020)
<3.0	3 (30%)
>3.0	7 (70%)

Figure 3. Comparison of CEA Levels when both Pelvic and Para Aortic Nodes are Present (p-0.020)

was taken as normal.

On Comparing CEA levels in Para aortic node positive patients, out of 21, 15 patients had CEA >3 ng/ml and 6 patients had CEA <3ng/ml which was statistically significant (p-0.002). (Table 1 and Figure 1).

In Pelvic Lymph node positive patient's node positive patients, out of 25, 12 patients had CEA >3 ng/ml and 13 patients had CEA <3ng/ml which was not statistically significant (p-0.777) as mentioned in Table 2 and Figure 2.

On comparing CEA values when both Para aortic and pelvic lymph node were involved, 70% of the patients with both pelvic and Para aortic node positive cases had increased CEA values and in Para-aortic lymph node present & pelvic lymph node absent cases 72.7% patients had increased CEA values which were highly significant (p-0.020) as mentioned in Table 3 and Figure 3.

Discussion

Concurrent chemo-radiotherapy (CCRT) is a proven treatment for locally advanced cervical cancer [19-24]. Lymph node involvement is the most important prognostic parameter for patients with cervical cancer. The presence of lymph node metastases significantly influences patient's outcome and therapeutic modalities more than any other clinical or pathological feature [25]. The latest FIGO staging system has incorporated lymph nodal involvement; hence, the importance of accurate lymph nodal assessment is compounded and has direct implications on the mode of management [15].

For patients at suspicion of Para-aortic and Pelvic lymph node involvement imaging for metastatic workup is recommended. There is no universally accepted diagnostic modality for the detection of PALN metastases. Positron-emission tomography-contrast-enhanced computed tomography (PET-CECT) and surgical staging via open/laparoscopic approach have failed to show a significant survival advantage [26,27]. Similarly, prophylactic irradiation of non-enlarged para-aortic nodes has a doubtful survival benefit [28].

Para-aortic lymph node (PALN) recurrence is not uncommon. The incidence of isolated PA nodal recurrences is 2-12 per cent, in radically treated cases of cervical cancer [29]. The approach to reduce PALN recurrence is a crucial problem for the treatment of locally advanced cervical cancer. Treatment options mainly include irradiating the PA chain to 45-50 Gy with or without a boost to the node or treatment of the gross node alone with stereotactic body radiation therapy (SBRT) [30]. Surgery may also be an option for those with previous irradiation to the PA region. Treatment of such patients could be an area of future investigation. Morris et al. conducted a randomized trial to examine entire pelvic CCRT versus extended field radiotherapy (EFRT). They located that CCRT improved overall survival and disorder-free survival, in addition to reduced loco regional and distant failure than EFRT. However, the 5-yr recurrence rate of Para-aortic lymph node (PALN) turned into 7% and 4% (p = 0.15) (Morris et al. 1999) [19].

CEA is a reliable tumor marker in patients with carcinoma of the cervix [17]. The presence of lymph node metastases has extra stated impact on the CEA values than the primary tumor [18]. The main aim of our study was to correlate the pretreatment CEA values and its association with Lymph node metastasis.

Disaia et al. did a study on a group of patients with carcinoma of the cervix and found that there was a progressive increase in the percentage of patients with positive CEA values correlating with advancing stage of the disease from 26% in stage I to 88% in stage II [31]. Incidentally 85% of the recurrent cases showed positive CEA values. Pre-treatment levels over 5 ug/l are highly suggestive of metastatic disease as they are associated with metastases in pelvic or Para-aortic lymph nodes in 50% of patients with stage IB disease. Also in advanced stages such as III and IV, 48% of patients had a pre-therapy value exceeding 5 ug/l [32]. Similarly in our study, we compared pretreatment CEA values with the incidence of lymph node metastasis which revealed 65.2% of the patients with high pretreatment CEA value had PALN metastasis.47.8% of the patients with high CEA had pelvic lymph nodal metastasis and 70% of the patients with high pretreatment CEA had both Pelvic and PALN metastasis which was statistically significant. Our results suggest that high CEA has direct correlation with the lymph nodal metastasis.

Patients with occult PALN micro metastasis are at risk for PALN recurrence if they undergo pelvic CCRT for CT-negative PALN metastasis. Hence, paraaortic lymphadenectomy can confirm subclinical PALN micro metastasis. Minimal complications are acceptable in modern laparoscopic technique. A large study (n = 253) reports that for 17.9% of patients with pathology confirmed PALN metastasis, their metastases were not detected in the CT scan at initial diagnosis of cervical cancer [33]. The false negative rate of CT detection was 23% in patients with laparoscopic extended para-aortic lymphadenectomy. Taken together, the false negative CT detection rates of around 20% are compatible with the current incidence of PALN recurrence (18.6%). This finding implies that PALN recurrence may result from suboptimal pelvic CTRT

without addressing Para aortic nodes. Hence, we suggest that screening for PALN metastasis in high-risk patients should be a priority, where CEA can act as an adjunctive procedure in addition to imaging and surgical procedures.

The main limitation of our study was the smaller sample size. Larger prospective randomized studies with larger population are needed for strong evaluation of efficacy and to draw inferences about the pretreatment CEA and its correlation with the Lymph nodal metastasis in Carcinoma Cervix patients.

In Conclusion, CEA has the capability of prognosticating Carcinoma cervix patients with the association of pelvic and Para-aortic nodes. In our Study, we found that CEA could be a useful marker in detecting nodal involvement in Carcinoma Cervix. This may be effective tool for detecting early failures, may help to salvage the unfortunate patients and give them a chance to prolong their survival with treatment like surgical debulking of para-aortic region and extended field radiotherapy.

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