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Prophylactic Para-Aortic Nodal Irradiation in Carcinoma Cervix: To Do or Not to Do?

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Introduction

The role of para-aortic lymph nodal irradiation (PALNI) remained undefined so far. Firstly, FIGO staging did not take nodal status into account hence the node positive patients remained an undefined subgroup. Secondly, despite RTOG trials establishing the survival advantage of prophylactic PALNI, it was not advocated due to the fear of adverse toxicity profile. The adoption of more conformal radiation techniques has revisited this issue. As with the recent advances in technology in imaging as well as the treatment techniques, there has been a tremendous improvement in treatment delivery leading to reduction in the incidence of acute as well as late toxicities. The interest in PALNI has also been triggered by the new FIGO staging which has defined and assigned a stage group to the pelvic and para-aortic LN positive cases. With this pretext in mind we review the current status of prophylactic paraaortic irradiation.

Undefined benefit for Para aortic LNI

Most of the evidence regarding extended field paraaortic radiotherapy (EFPRT)is from the pre concurrent chemo radiation era. Haie et al. [1] reported that prophylactic PALNI significantly reduced incidence of para aortic and distant metastases (DM). But, the incidence of late toxicities was higher in EFPRT group compared to whole pelvis radiation therapy (WPRT) group (9% versus 4.8%). Rotman et al. [2] updated results of a prospective randomized RTOG trial that demonstrated that elective PALNI improved 10-year overall survival (55% versus 44%, p=0.02) and decreased DM with no difference in local recurrence and diseases free survival. Ten-year grade IV/V complication rate in EFPRT arm was 8% and in the WPRT arm was 4%. Despite high rates of late complications, EFPRT was beneficial in the pre concurrent chemo radiation (RTCT)era.

However, with concurrent RTCT becoming the standard of care from 1999 onward, the role of EFPRT alone in locally advanced carcinoma cervix has become unclear. Morris et al. conducted a prospective randomized control trial that compared EFPRT without concurrent chemotherapy versus WPRT along with concurrent chemotherapy [3]. Results reflected overall survival better in the patients receiving concurrent RTCT. The possibility of extended field radiation with concurrent chemotherapy has been evaluated and administered to patients in certain trials but the most important issue was the higher toxicity profile. In a study by Sood et al., EFPRT with concurrent chemotherapy followed by brachytherapy produced substantial acute toxicities but its long term, toxicity profile and primary tumor control were excellent [4].

Here, the superior border of the radiation field extended up to L1-L2 disc space. All the 54 patients in the study received 45Gy over 5 weeks to pelvis and para aortic lymph nodes. Almost 81% of patients received concurrent chemotherapy with cisplatin while 19% did not receive any chemotherapy. In both the groups para aortic lymph node recurrence was not observed during follow up. Acute toxicities (>/= Grade III gastrointestinal, genitourinary, hematological) were higher in patients receiving concurrent chemotherapy. Incidence of late toxicities (intestinal obstruction, rectal bleed) with chemo is 6% and without chemo is 10%. This study reported that EFPRT with or without concurrent chemotherapy but followed by brachytherapy had a survival rate of 80%, local control rate of 85%, distant metastases free survival rate of 95% and the incidence of late complications was low.

Asiri et al. [5] showed that prophylactic EFPRT with concurrent chemotherapy could be a reasonable option for patients with locally advanced cervical cancer with radiologically positive pelvic lymph nodes and negative para aortic lymph nodes. Similarly, Lee et al. [6] reported a prophylactic lower para aortic radiotherapy with IMRT technique with concurrent weekly cisplatin for FIGO stage IB2-IVA carcinoma cervix. In their study, paraaortic LN recurrence free survival for WPRT versus EFPRT was 80.1% versus 96.4% (p=0.02) and overall survival for WPRT versus EFPRT was 58.1% versus 83.5% (p=0.01).

The initial trials had incorporated para-aortic nodal staging before recruiting patients for concurrent RTCT. Subsequently as more and more functional imaging was employed for nodal

staging. But the sensitivity and the specificity of the paraortic lymph node (PALN) detection has not been high. Studies have tried to establish the concurrence rate of the PETCT and surgical staging. The findings have suggested that in as many as up to 22% the PETCT is unable to detect the paraaortic lymph nodes. These undetected lymph nodes act as a sanctuary site as they are neither addressed surgically or by radiation therapy. There are no means other than a paraaortic LN dissection or a sentinel lymph node biopsy to detect these nodes but are currently not advocated and are still under investigation.

The paraaortic LN may be addressed are by prophylactic irradiation, but there is a need to define the patients who would benefit from the prophylactic therapy. Most common prognostic factors for which PALN irradiation is reasonable are cases with pelvic lymph nodes i.e. stage IIIC1 disease. As in this subgroup the chances of harboring paraaortic lymph nodes is higher. The most dreaded side effects of PALN irradiation includes small bowel toxicity including duodenal ulceration. It is recommended to contour paraaortic volumes conservatively especially when these volumes are close to small bowel. In vessel-based contouring the margin expansion from aorta of 10 mm circumferentially except 15 mm laterally is created and expansion from the IVC of 8 mm anteromedial and 6 mm postero-laterally is created to define the paraaortic nodal stations [7]. Additionally editing of the PTV to reduce the volume of duodenum in the high dose gradient is also permitted. So, employing conformal techniques like IMRT with precise volume definition can reduce the dose to small bowel dose.

Redefining the superior border of prophylactic PALNI

Definition of the superior border of the prophylactic para-aortic field has also witnessed a change in the last 2 decades. From the liberal volumes extending from D10 vertebral levels there is an increasing practice of irradiating para aortic LNs up to the infra-renal region. The basis of doing only infra renal paraaortic LN irradiation is that the lymphatic ducts drain into the cysterni chylii which is located below the renal hilum (corresponding to the L2 vertebral) level. And most of the lymph node failures are encountered below the renal hilum. Sparing the area above the renal hilum leads to reduction in small bowel toxicity and improves the treatment tolerance.

Semi extended field radiotherapy with concurrent cisplatin -the order of the day

Attempts have been made for decreasing the radiation field and still obtaining the prophylaxis at para aortic lymph nodes. A study conducted by Jie Lee et al. showed that PALN recurrence decreased with sub renal vein prophylactic radiotherapy (semi extended field-SEF) using IMRT technique with tolerable toxicities supporting the application of risk based radiation fields for carcinoma cervix.6 In this study, 76 women were treated with SEF-IMRT to a dose of 50.4Gy/28 fractions along with concurrent chemotherapy with cisplatin followed by brachytherapy. The nodal clinical tumor volume (CTV) included presacral region, regional lymph nodes (common, internal and external iliac lymph nodes) and para aortic lymph nodes to the level of renal vessels. The 5-year para aortic recurrence free survival in WPRT versus SRVRT is 87.6% versus 97.9% (p=0.03) and overall survival in WPRT versus SRVRT is 74.5% versus 87.8% (p=0.04). No patients had acute genitourinary toxicities of any grade, while 2 patients had acute grade III or greater gastrointestinal toxicity (2.6%) and 41 patients had acute grade III or greater hematological toxicities (53.9%). Three patients had late grade III gastrointestinal toxicity, and none had any late genitourinary toxicities.

Hence, it has been concluded that prophylactic semi extended field (below renal vessels) IMRT is better than conventional prophylactic EFPRT for locally advanced carcinoma cervix both in terms of overall survival and toxicity profile. Main failure sites of SEF-IMRT were distant and were out of the radiation field. Beadle et al. [8] described most common site of regional recurrence was marginally above the superior boundary of pelvic field. Kuku et al. [9] found that EFPRT was a significant factor predicting the severity and chronicity of the ongoing disease in patients who developed bowel injuries after treatment for carcinoma cervix. Another study that evaluated SEF using a conventional technique along with concurrent chemotherapy was done by Choie et al. [10] which also showed favorable para aortic lymph node control and survival outcomes. Hence, with the use of IMRT technique and the radiation field below renal vessels (semi extended field), along with concurrent chemotherapy for locally advanced carcinoma cervix, treatment outcomes are favorable with acceptable acute and late toxicities. With the use of SEF-IMRT, failure predominantly is in the distant sites and hence, the possibility of modified and intense chemotherapy has to be investigated further.

Conclusion

In the era of conformal radiation therapy, the feasibility and the tolerability of the PALNI has improved. With integration of imaging into staging, planning as well as verification the acute toxicities can be reduced substantially. Many studies have incorporated the prophylactic semi-extended paraaortic LN irradiation into the treatment protocol in order to reduce the eminent risk of PA LN failure without adding to morbidity. By modifying the field of radiation to exclude para aortic lymph nodes above the level of renal vessels to reduce toxicity without compromising the treatment outcomes prophylactic paraaortic lymph node irradiation can be safely practiced.

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