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REVIEW ARTICLE

Role of Radiotherapy in Differentiated Thyroid Cancer

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ABSTRACT

Differentiated thyroid cancers (i.e. papillary or follicular) account for majority of thyroid malignancies. Even though surgery has been the mainstay for these tumors, use of radioactive iodine (I^{131}) therapy and thyroid hormone replacement therapy is common in most of these tumors in adjuvant setting. Radiotherapy is indicated in the presence of, gross residual disease after surgery, extra-capsular extension, and extensive lymph node involvement. As thyroid gland is located at the root of neck, sometimes with retrosternal extension and surrounded by critical structures, it is difficult to adequately cover the entire target volume with conventional radiotherapy technique. IMRT is a useful technique in these tumors, since it provides good dose distribution along with sparing of spinal cord while treating thyroid bed in adjuvant setting, and therefore it needs to be further standardized. Additionally palliative radiotherapy is effective in brain and bone metastasis. To conclude, external beam radiotherapy is an established and effective mode of therapy both in curative and palliative settings.

Keywords: Vocal fold, Palsy, Adductor palsy, Thyroidectomy, Recurrent laryngeal nerve.

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INTRODUCTION

Thyroid cancers are derived either from follicles or epithelial unit of thyroid gland. Histopathological classification is largely based on these two cell systems. They are either papillary (which includes mixed papillary-follicular), follicular, medullary and anaplastic type.

Ninety percent of the thyroid malignancies are differentiated variety, i.e. papillary or follicular subtype.[1] Pure follicular carcinomas have a greater tendency toward local invasion and hematogenous metastasis. Papillary carcinomas and mixed variety, on the other hand, are more likely to involve the lymph nodes.[2] Overall, the prognosis remains age dependent, i.e. patients presenting at younger age fare better than the older ones.[3] Increased age at diagnosis and widespread metastatic disease are associated with poor prognosis, independent of the cancer variety. The overall survival rates, corrected for age and sex, are 98% for papillary and 92% for follicular cancer.[3] Surgery is the mainstay of such tumors yielding 90% long-term results.[4] There are two potential surgical approaches to these thyroid cancers: total (or near total) thyroidectomy and unilateral lobectomy along with isthmusectomy. Subtotal thyroidectomy, is considered to be an inadequate procedure and is not recommended. Radical neck dissection has been abandoned in favor of limited dissections for metastatic lymphadenopathy. Prophylactic neck dissection is no longer used.[5]

Current adjuvant treatment strategies are based on retrospective series only, as these tumors are infrequent and randomized evidence is not possible. Radioactive iodine (RAI) therapy and thyroid hormone replacement therapy have been used in all these tumors in adjuvant setting since the 1940s. The role of radioactive iodine is to ablate the remnant tissue outside the thyroid bed.[6] It is increasingly being recognized in adjuvant setting in these tumors. Role of external beam irradiation in differentiated thyroid carcinoma depends upon I^{131} uptake after surgery. Most of these tumors concentrate I^{131} sufficiently, so that therapeutic doses can be administered. External beam radiotherapy (EBRT) may be used after I^{131} treatment is nonfunctional (i.e. does not accumulate I^{131}). This state may be attained in case of recurrent cancers where it becomes less differentiated and less functional. Other indications are: (i) there is gross residual disease in the surgical field, (ii) extracapsular extension, and (iii) extensive lymph node involvement. Radiotherapy has also been used in palliative setting especially in bone and brain metastasis.[7,8]

These tumors have been stratified into high, intermediate and low risk categories and the line of management is based on the risk category of the patient. Radiotherapy is used in adjuvant setting, in high risk situations.[9] These are as follows – age >45 years, males, tumor size >4 cm, extra thyroidal extension, high grade tumors and presence of distant metastasis. Several retrospective analyses have shown that addition of external beam radiotherapy to residual disease improves the local relapse free rate, especially in older (>40 years) patients.[10-12] Similarly, it has been observed that radiotherapy when given in presence of gross residual or inoperable disease, increases the locoregional control rate three fold, but not cause specific survival or overall survival.[13] Tsang et al from Princess Margret Hospital, Toronto, Canada showed a similar benefit in local recurrence free survival rate in microscopic residual disease, i.e. R1 resection.[8] Inoperable bulky disease may also be approached with curative intent in these tumors.

Most of the large retrospective audits, that have used radiotherapy to treat DTC, have used in high risk situations. All report local control in the range of 80 to 90% at 4 years.[10,12] Based on the abovementioned reports, American Thyroid Association (ATA) have advised radiotherapy to be considered in extrathyroid extension at the time of surgery, and for patients with gross residual tumors in whom further surgery or RAI would be ineffective, in their revised guidelines.[14] British Thyroid Association (BTA) in addition suggests the use of radiotherapy in extensive extranodal spread, after optimal surgery, even in absence of evident residual disease.[15] As regards the sequencing of EBRT and RAI, in the situations that merit adjuvant radiotherapy, ATA advises the basis of presence of gross residual disease and likelihood of the tumor being RAI responsive.[14,16]

As regards palliative setting, radiotherapy to bone metastasis gives a durable response in terms of stability of bone and pain palliation, in around 80% cases, using single fraction of radiotherapy. This is contrary to the data from series that have used RAI for bone metastasis, where although 60% bone metastasis have shown to have I^{131} uptake, but only 3% respond.[17] Chin et al (1997) from MD Anderson Hospital showed that adding whole brain radiotherapy to resected solitary brain metastasis in DTC improved the median survival to 12.4 months.

RADIOTHERAPY PORTALS, DOSES SCHEDULES AND TECHNIQUES

The treatment field should include entire thyroid tumor bed, neck and superior mediastinum. Earlier, postoperative radiation was given using conventional anteriorposterior fields. An anterior portal was used to cover the thyroid bed and draining lymph nodes in the neck. Posterior mediastinal field was given to boost the midmediastinal tumor (retrosternal extension). A dose of 60 in 30 fractions is recommended in postoperative situations. Realistically, a dose of 50 Gy in 25 to 28 fractions can be delivered over 5 to 5½ weeks by this technique so as to respect the dose limiting spinal cord. Further dose to gross residual or inoperable disease can be attempted as a boost to deliver a total dose of 70 Gy (i.e. 20 Gy beyond the large field of 50 Gy). Small oblique fields are placed to irradiate thyroid (or bed) alone and simultaneously ensure that the spinal cord does not come into the beam trajectory. Boost fields are technically challenging and may not be possible to deliver in all situations (Figs 1A to D).

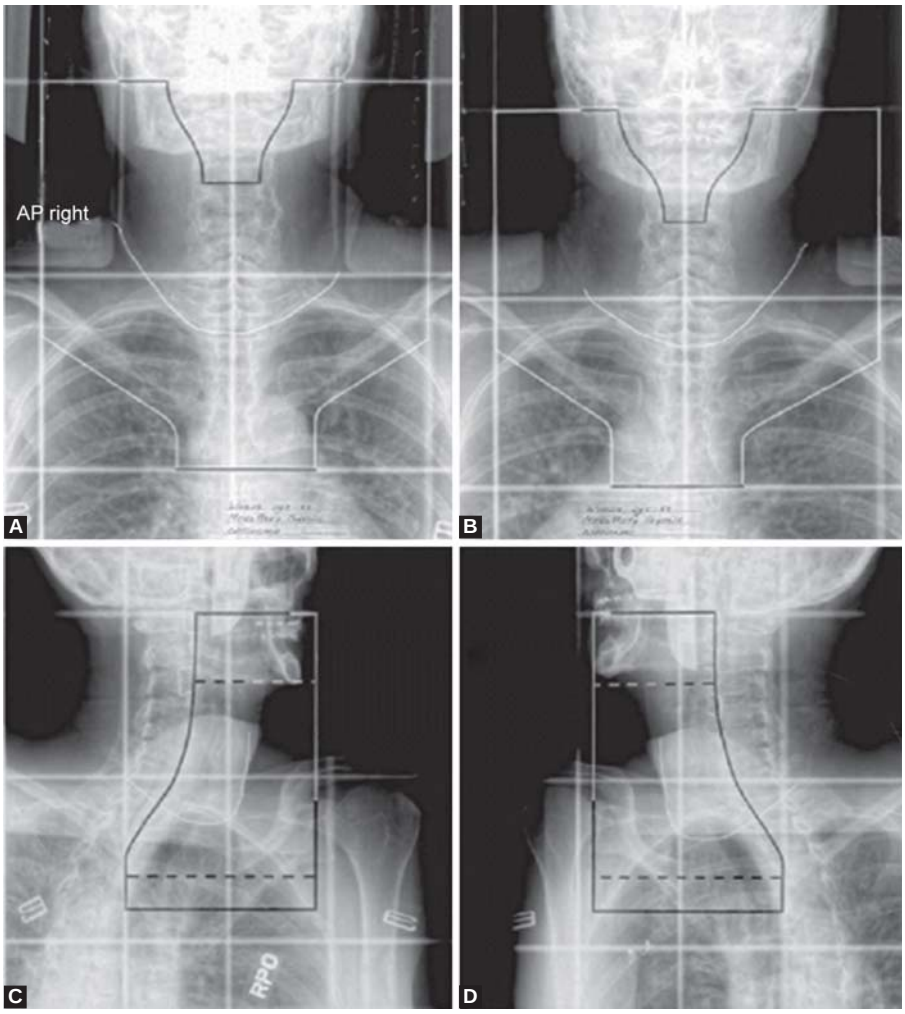
Intensity Modulated Radiotherapy (IMRT) is a technique for delivering optimized nonuniform beam intensities to the target volume of almost any shape, thereby providing a new approach to the whole treatment procedure from patient immobilization to beam delivery. It aims at increasing the radiation dose gradient between the target tissues and the surrounding normal tissues at risk, thus increasing the locoregional control probability while decreasing the complication rate. As a prerequisite, IMRT requires a proper selection and delineation of target volumes. Thyroid malignancy is one site, where use of IMRT has been found to be especially useful. This is because of the anatomical location of the thyroid gland, irregular contour of the neck region, retrosternal extension of the tumors, presence of the bone and air in the vicinity of the tumor/thyroid bed (leading to dose perturbation) and most importantly the proximity of the gland to spinal cord. IMRT offers good dose distribution to the thyroid bed and respects the spinal cord as a dose limiting structure (i.e. dose not to exceed 45-50 Gy). With the use of IMRT, it is possible to deliver higher dose, i.e. 70 Gy to gross inoperable disease, 60 Gy to microscopic disease and 45 to 50 Gy to the subclinical disease that the lymph nodes in the neck are likely to harbor.

Most patients merit radiotherapy to thyroid bed (including tracheo-esophageal groove) and adjoining lymph node areas from hyoid to aortic arch (level VI being the first lymph node station, followed by level IV, VII and lower V group of lymph nodes).[16] In case of the extranodal spread and presence of multiple lymph nodes at multiple levels, the radiotherapy portals are extended superiorly covering level II and III group of lymph nodes also. IMRT is a particularly useful technique in the latter scenario, as it may allow sparing of the parotid glands as well[12] (Fig. 2).

While IMRT technique has brought a dramatic change in radiation delivery in thyroid cancers, it is important to remember that this technique has a definite learning curve and is labor intensive.[12] It requires good immobilization, thin CT scan slices with good intravenous contrast material followed by target volume delineation and multitrajectory beam planning. This requires streamlining of departmental protocols and quality assurance of each of these aspects of radiotherapy treatment delivery.

Painful bony metastasis can be palliated by EBRT. Prevention of pathological fracture especially in weight bearing sites is another important goal. Single fraction of 8 Gy is an effective and useful dose schedule in an Indian context in such situations.

Progressive metastasis in the brain tends to compress upon the vital structures. The life expectancy with brain metastasis is under 3 months. Palliative RT to the whole brain helps in alleviating compression to these structures and increases the life expectancy to 6 to 9 months. A dose



Figs 1A to D: Conventional postoperative radiotherapy planning: An opposed anterior and posterior (AP-PA) technique with shielding for the anterior field was used to treat the initial target volume (A and B). The wire indicates the surgical scar. A dose of 44 Gy is delivered in 22 fractions following which the left anterior and right posterior oblique fields (C and D) are used to boost the tumor bed and right neck. After reaching a tumor dose of 50 Gy, the length of the oblique fields is reduced to encompass the areas of known tumor involvement for an additional 10 Gy. Therefore, the primary tumor bed and involved nodal areas received a total dose of 60 Gy, the right neck received a dose of 50 Gy, and the contralateral neck and mediastinum received a dose of 44 Gy

of 20 Gy in 5 fractions or 30 Gy in 10 fractions over 2 weeks, under steroid cover, is adequate to achieve palliation. Patient's performance and ambulatory status needs to be considered in selecting the proper dose schedule.

ROLE OF CHEMOTHERAPY

Chemotherapy is a treatment option for patients with metastatic DTC that are nonresponsive to radioiodine and TSH-suppressive thyroid hormone therapy. The data is however historical and limited. Newer targeted chemotherapies have emerged as effective alternatives for progressive disease, although most remain investigational.

Multitargeted kinase inhibitors that directly inhibit the activity of the tyrosine kinases have been successful in treating some cancers, and they hold promise for the treatment of refractory metastatic DTC. It is preferable to enroll patients in clinical trials of therapies targeting the molecular and cellular pathogenesis of DTC, for unresponsive or symptomatic metastatic DTC. For patients with metastatic unresponsive DTC (tumors >1 to 2 cm and growing by at least 20 percent/year) or symptomatic metastatic disease who are unable to participate in clinical trials, may be started on an oral tyrosine kinase inhibitor, such as sorafenib or vandetanib, rather than a cytotoxic agent. Single agent doxorubicin is an effective alternative for patients who are unable to afford or tolerate kinase inhibitor therapy.[9,18] The recommended dose is 60 to 75 mg/m^2 every 3 weeks. The combined results of ten

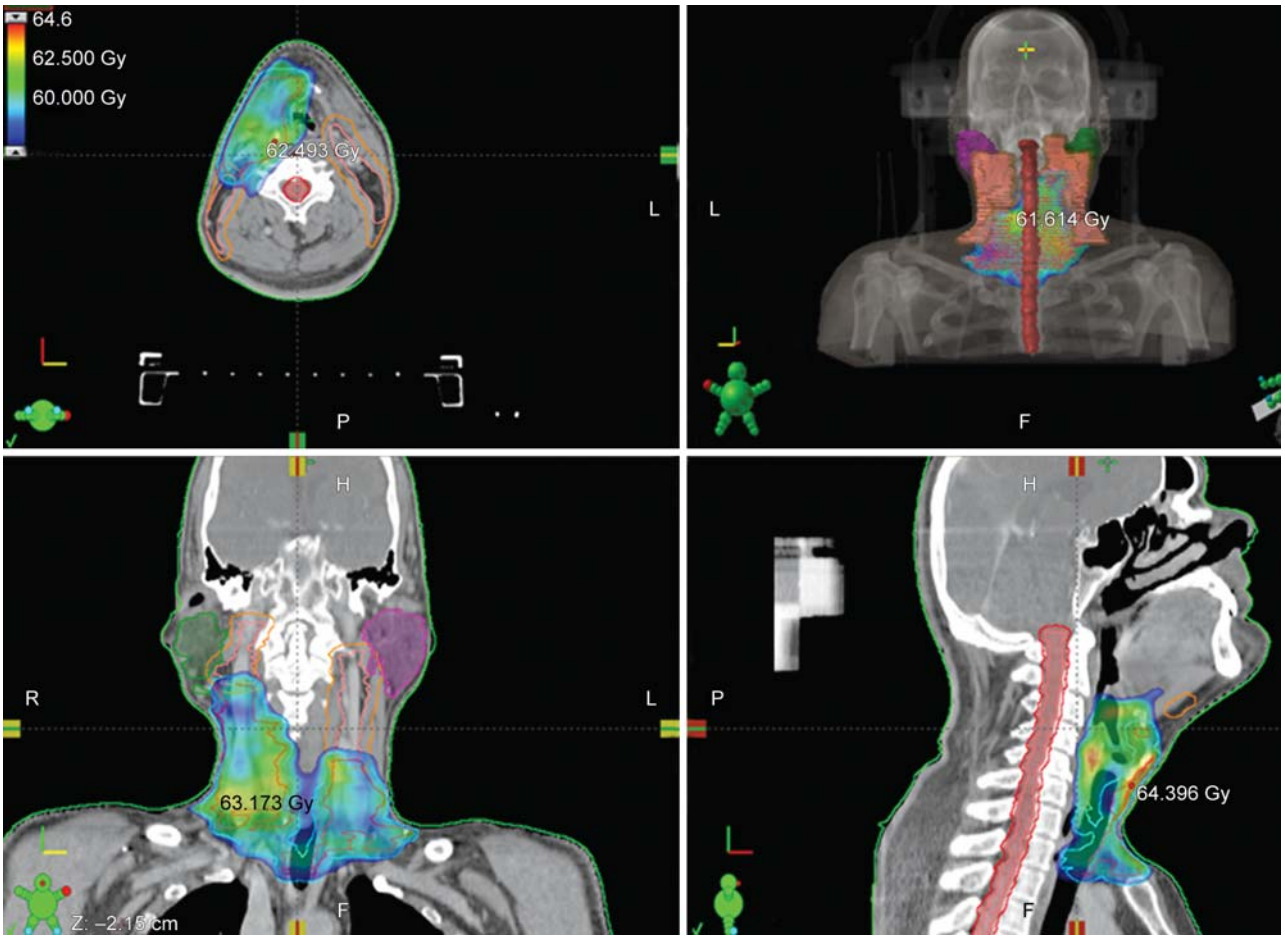


Fig. 2: IMRT treatment planning: Transverse, frontal, sagittal and digitally reconstructed radiograph (DRR) based planning images of a 50 years old papillary carcinoma thyroid patient. Contours of CTV1 (60 Gy, blue) and CTV2 (54 Gy, orange) and isodose curves are shown

published reports shows that doxorubicin is associated with a response rate of up to 40% for progressive differentiated cancers that do not respond to radioiodine, including Hurthle cell carcinoma, but most responses are incomplete and transient.[19]

CONCLUSION

To conclude, the role of EBRT in DTC in adjuvant setting is increasing. Radiotherapy has a role in palliation of bone and brain metastasis. IMRT offers good dose distribution and sparing of spinal cord while treating thyroid bed in adjuvant setting, and therefore needs to be standardized in these tumors. Chemotherapy, i.e. single agent doxorubicin or tyrosine kinase inhibitors have been tried in metastatic DTCs with some response.

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