

The Place and the Role of Radiation Therapy in the Treatment of Thymic Carcinoma

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Abstract

Thymic carcinomas arise from the epithelial cells of the thymus gland and are the most common tumors of the anterior mediastinum despite their overall rarity. Because of their rarity, their treatment remains a challenging topic. Although historically they have been treated surgically, radiation therapy (RT) has an important role either as a definitive or as a postoperative treatment. In this article, we present a review of the current therapies for the thymic carcinomas and try to identify the exact place of the RT in the optimal management of these patients.

Keywords: Thymic carcinoma; Radiation therapy

Introduction

Thymic malignancies are the most common primary neoplasms of the anterior mediastinum; however, they are a relatively rare disease. They usually occur in patients aged 40 - 60 years with a male to female ratio of 1:1. Thymic carcinomas arise from the epithelial cells of the thymus gland and are classified into six subtypes from the Masaoka clinical staging system [1] and the World Health Organization (WHO) [2]. They grow in close proximity to critical structures like heart, lungs and great vessels; hence, it is very difficult to treat without causing great morbidity to patients.

Up to 40% of thymoma patients present no symptoms. Common signs and symptoms are caused by local invasion of the disease or paraneoplastic syndrome, especially myasthenia gravis. Other commonly observed signs in thymic carcinomas

include chest pain, dyspnea, dysphagia, cough and superior vena cava obstruction [3].

Treatment of thymoma depends on the respectability of the disease and surgery is the mainstay of therapy [4]. Completeness of resection is prognostically significant. Radiotherapy (RT) has long been established as an important component in the therapy of this disease, although its outstanding benefit versus toxicity in the postoperative setting remains debatable [5]. The evolution of the RT from 3D conformal treatment to four-dimensional (4D) treatment, intensity modulated radiation therapy (IMRT) and proton use has led to less toxicity and better control of the tumor [6].

Adjuvant RT

Postoperative RT (PORT) should be considered for various indications. There are no phase III studies investigating adjuvant treatment but adjuvant RT is recommended following incomplete excision of stage II and III tumors [7]. Radiation for R1 or R2 thymic malignancies should be started within 3 months of surgical resection. Doses between 40 and 64 Gy are most appropriate for microscopically positive margins, whereas doses of 54 Gy or higher should be used for gross disease. Patients with positive margins should be considered for concurrent RT and chemotherapy [8].

In completely resected (R0) thymic malignancies, RT should be considered more strongly as the risk of recurrence increases. Some of the indications are aggressive tumor histologies or Masaoka stage II and III disease [9]. The minimum acceptable dose for postoperative R0 disease is 50 Gy with standard fractionation 1.8 - 2 Gy/day.

Radiation to elective nodal region is not recommended, while the extend of the malignancy before the surgery should be used as a guide for the delineation of the target volumes [5].

Neo-Adjuvant RT

When the disease appears to be unresectable at diagnosis, neo-adjuvant chemotherapy and RT can increase the likelihood of resection for patients who are otherwise eligible for surgery. RT in this context can be difficult to deliver without exceeding dose constraints and it should include the gross area of

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involvement with an appropriate margin [10]. The dose for neo-adjuvant RT should be 45 Gy in 1.8 Gy daily fractions.

Definite RT

Definite RT is preferred for patients who are not candidates for surgery because of the extent of disease during the diagnosis or because they are unfit for surgery due to medical conditions [11]. The control of the disease is more achievable with the combination of RT and chemotherapy. The radiation dose should be 60 - 66 Gy to encompass the gross disease plus a margin for microscopic regions at risk.

Target Volume Delineation and RT Techniques

The multidisciplinary team plays an essential role in the delivery of RT so as to assure the maximum benefit and the less toxicity for the patient. Discussion with the surgeon and the pathologist is very important to define sites at risk of local recurrence [12]. The delineation of the gross tumor volume (GTV) is defined if there is residual macroscopic disease. GTV is expanded isotropically by 10 mm to form the clinical target volume (CTV) so as to encompass the microscopic disease. If chemotherapy has been given, the CTV should encompass all initial sites of disease and possible sites of microscopic invasion which may include the mediastinum and pericardium. The CTV is then expanded by 5 mm to form the PTV so as to include the systematic and random errors and the organ motion [13].

Because of the central location of these malignancies, the use of 3D CRT, IMRT or, if available, proton beam therapy, is strongly recommended. Adaptive re-planning should also be considered, because of the important change in the size and shape of these tumors during the several weeks of the course of radiation treatment. This includes obtaining an additional CT halfway through treatment and re-evaluating the tumor coverage; hence, we can significantly minimize the radiation dose to normal tissues [14].

Inverse planned IMRT may enable the delivery of higher doses of radiation, increase the probability of disease control and limit the dose to the surrounding esophagus, spinal cord, heart and lung [15].

Discussion

Because of the rarity of the disease, there is a lack of studies which evaluate whether the inclusion of RT affects disease control and survival in thymic malignancies.

Currently, the role of adjuvant RT in the treatment of thymic malignancies largely depends on the stage of the disease and the extent of surgical resection. Patients with stage I or stage II, R0 or with favorable histology (WHO class A, B, B1) seem to have no benefit with the addition of RT [16].

In contrast, patients with stage III and IV disease and other unfavorable factors seem to benefit in terms of survival, local

control or recurrence upon the addition of RT after surgical resection [17].

More data are necessary to establish a definite algorithm for treatment and radiation- dose relationship as well as the incidence of toxicity from treatment. It is important to follow patients carefully so as to monitor for signs of recurrence and late toxicity from RT.

In conclusion, a great deal of concern should be given in the development of multicenter, randomized studies/trials which will provide the scientific community with evidence-based treatment algorithms for thymic malignancies.

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