JBUON 2017; 22(6): 1385-1389
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

REVIEW ARTICLE

Stage-II thymoma and emergency coronary artery bypass. To irradiate or not to irradiate to avoid radiation induced vascular injury? Case report and literature review

Ilias A. Kouerinis[1]*, Maria Tolia[2]*, Flora Zagouri[3], Michail Nikolaou[4], Nikolaos Tsoukalas[5], George Kyrgias[2], Meletios A. Dimopoulos[3], Charalambos Vlachopoulos[1], Ioannis Karathanassis[1], Christina K. Zoubouli[6], Ioanis Kokakis[7], Vasileios Kouloulias[7], Konstantinos Triantafillou[1]

[1]First Department of Cardiothoracic Surgery, Hippokration University Hospital, Athens, Greece; [2]University of Thessaly, School of Health Sciences, Faculty of Medicine, Department of Radiotherapy, Biopolis, Larissa, Greece; [3]Department of Clinical Therapeutics, Alexandra Hospital, Medical School, University of Athens, Athens, Greece; [4]Department of Internal Medicine, Oncology Unit, Hippokration University Hospital, Athens, Greece; [5]Oncology Clinic, 401 General Military Hospital, Athens, Greece; [6]Department of Pathology, Hippokration Hospital, Athens, Greece; [7]First Department of Radiology, Radiotherapy Unit, Aretaieion University Hospital, Medical School of Athens, Greece

*These authors contributed equally to this work

Summary

Purpose: *The purpose of this study was to present the controversial role of adjuvant radiotherapy to a 72-year-old male patient with Masaoka stage II thymoma and coronary artery bypass and to review the relevant literature.*

Methods: *The data were collected by relevant studies on PubMed and EMBASE. Articles up to March 2017 were included.*

Results: *Although the radiation-induced vascular injury to the internal thoracic artery and its suitability for grafting in a patient who is candidate for coronary artery bypass is documented, the possible catastrophic effect of adjuvant radiotherapy to existing grafts in a patient with prior bypass surgery has not been fully investigated.*

Conclusion: *The application of radiotherapy in a patient with R0 stage II thymoma is currently considered of 2B level of evidence but its potential occlusive effect to an underlying coronary graft may dramatically affect the survival of the patient and accordingly drop the level of evidence of its use.*

Key words: *coronary artery bypass, radiotherapy, thymoma, vascular injury*

Introduction

Thymoma is an uncommon malignancy (1.5 cases/million) with an overall incidence of 0.13 per 100,000 person-years in the USA [1,2]. The 5-year survival rate is about 78% [3]. Although surgery remains the main therapeutic modality, adjuvant radiotherapy (RT) has also been recommended in order to reduce the rate of local and regional relapse after incomplete or complete resection [4-8]. According to the current NCCN Guidelines criteria (v. 3.2016), the application of postoperative RT

Correspondence to: Maria Tolia, MD, Msc, PhD. University of Thessaly, School of Health Sciences, Faculty of Medicine, Department of Radiotherapy, Biopolis, 41110 Larissa, Greece.
Tel: +30 6945472195, +30 2413502054, E-mail: martolia@med.uth.gr
Received: 02/07/2017; Accepted: 18/07/2017

in a patient with R0 stage II thymoma is considered 2B level of evidence [9]. Of note, vascular injury to vessels after RT has been well described in literature [10]. RT's potential occlusive effect to an underlying coronary graft may affect the survival of the patient. To irradiate or not to irradiate? This all common therapeutic dilemma which is applied in most oncologic patients seems to become clear when oncologists follow the current NCCN guidelines and/or well established therapeutic protocols. Nevertheless, the balanced decision towards or against the application of adjuvant mediastinal RT in a patient with underlying arterial and vein coronary grafts has not been studied in detail in the existing literature.

Herein, we present a patient with Masaoka stage II thymoma after complete tumor resection to determine the role of adjuvant RT and the possible acute and chronic effects of RT on the vasculature of arterial and vein coronary graft.

Case presentation

A 72-year-old male patient was referred to the cardiothoracic department of Hippokration University Hospital, Athens, hemodynamically unstable with the diagnosis of triple vessel disease and anterior mediastinal tumor diagnosed with chest x-ray (Figure 1). Due to his critical condition further CT exams were considered as time-consuming and therefore, the patient was prepared for emergency coronary artery bypass (CABG) surgery and excisional biopsy of the tumor, if possible. Written informed consent was obtained by the patient. After sternotomy a large, bulking, solid, capsulated tumor was found in the exterior right pericardial aspect (Figure 2). The mass was compressing exteriorly the right ventricle mimicking the pathology of tricuspid valve stenosis. Its complete excision was successful (Figure 3) and metallic clips were placed at the bed of its resection. The following CABG operation was completed in the standard fashion with the use of extra corporeal circulation, cooling of the patient in 34°C and without use of heart-lung suction to avoid any possible spillage of neoplasmatic cells into the circulation. The left anterior descending artery was bypassed with the

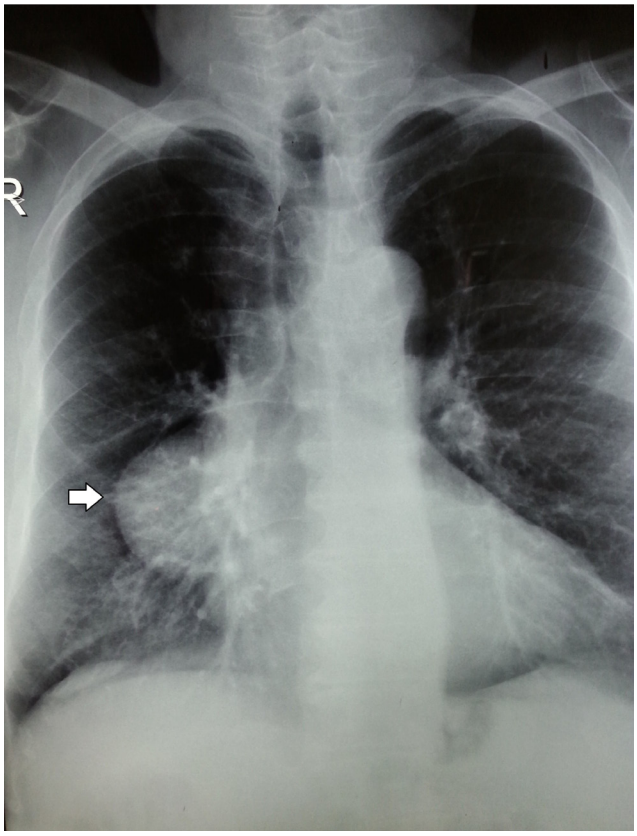

Figure 1. Anterior mediastinal tumor (arrow) diagnosed with preoperative chest x-ray.

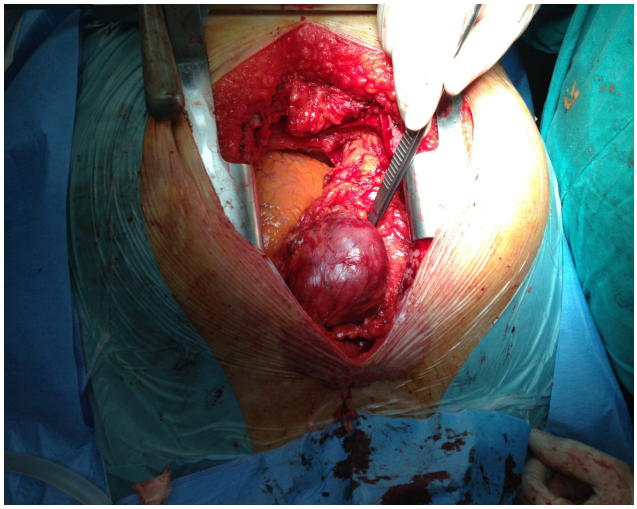

Figure 2. The excision of the spherical mass was not challenging and the right phrenic nerve was preserved.

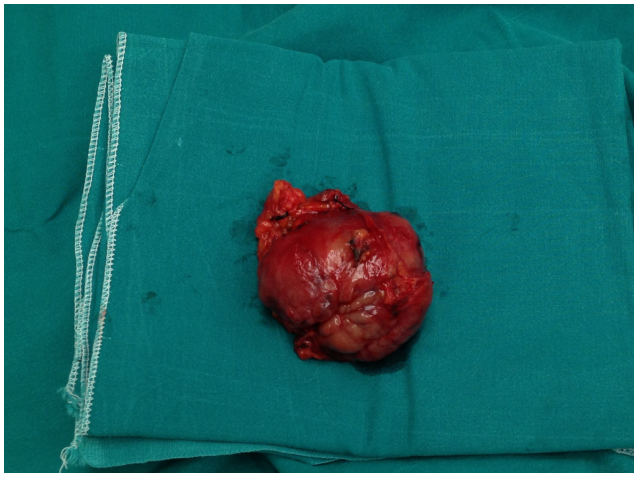

Figure 3. The intraoperative findings. After the excision of the thymoma, the right coronary artery to posterior descending artery graft was running through the bed of the tumor resection and its direct radiation was considered unavoidable in case of radiotherapy.

left interior thoracic artery and the posterior descending artery was bypassed with a saphenous vein conduit with part of its course running the bed of the resection. The patient experienced an uneventful recovery and was discharged home on the 6th postoperative day. The permanent sections (Figure 4) set the diagnosis of stage II thymoma and the adequate resection margins were proven microscopically and with positron emission tomography (PET) as well. The patient was referred to the radiation oncologists in order to review the operative findings and determine the target volume at risk.

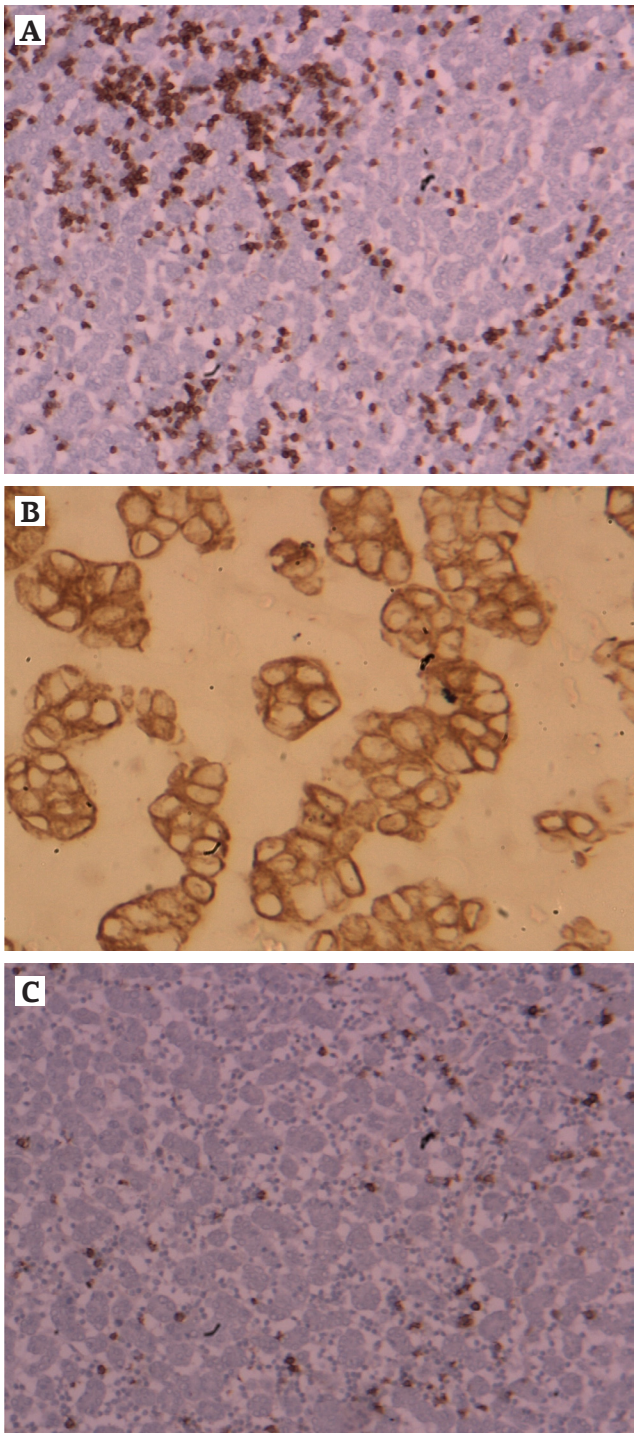

Figure 4. A: The permanent sections set the diagnosis of thymoma type A-AB with predominantly T lymphocytes and few B lymphocytes (original magnification x100). **B:** Islands of thymoma cells (KER 5/6 positive, x200). **C:** Thymoma type A-AB with few B lymphocytes (CD20 positive, x100).

Discussion

The delivery of adjuvant RT in a patient who has undergone coronary surgery raises two major concerns: the radiation-induced vascular injury (RIVI) to the existing grafts and the acceleration of the progression of the coronary artery disease itself. The radiation-induced vascular injury has been demonstrated in various studies but, concerning the coronary conduits, little is known. The possible mechanisms of RIVI are the following: a) Ischaemic necrosis due to occlusion of the vasa vasorum (blood supply of the large vessels, located in the outer arterial wall layer of adventitia). b) Extrinsic compression because of the adventitial fibrosis. c) Acceleration of classical atherosclerotic process [11]. d) Necrosis and fibrosis in the media and adventitia layers as a sequence of inflammation of endothelial cells [12]. The time interval from RT represents a significant risk factor related to RIVI.

The role of adjuvant irradiation for invasive thymomas has not been evaluated in a prospective randomised trial [13], however RT can be considered after a R0 resection in case of capsular invasion (category 2B recommendation) [9,14-18]. This arguing therapeutic effect has to be balanced against the probable sacrifice of the underlying coronary grafts. Obviously the more important the jeopardised from RT graft (e.g. a left internal thoracic artery to the left anterior descending coronary artery), the weaker the indication for irradiation. Nevertheless, no studies have investigated the radiation resistance of vein vs arterial grafts or that of a skeletonised vs a pedicled mammary graft. In a metanalysis that included the data from 592 staged II or III thymic epithelial, completely resected cases, there was no statistically significant difference in recurrence after adjuvant RT (odds ratio 1.05; 95% confidence interval: 0.63 to 1.75; p=0.840) [14]. Based on the results of this study we concluded that there was no indication for RT in our patient despite the fact that the jeopardised graft was of secondary importance (vein graft to a co-dominant right coronary artery). Towards our decision for a "watchful waiting" policy against RT was also the small time interval between the operation and the delivery of RT. The more recent the operation, the more vulnerable

are the underlying conduits and the anastomosis to the RT due to the potent inflammatory procedure. We estimated that the fibrosis of the vein graft and anastomotic stricture would be accelerated if we would administer RT even in low doses. On the other hand, waiting for a rational period of six months or more for the traumatic anastomotic edges to be healed and complete the endothelisation before RT was considered as unreasonable. All thymoma patients should be treated with modern techniques such as 3D-conformal RT (3DCRT) or intensity modulated RT (IMRT) in order to improve the dose distribution and minimize the dose to the adjacent critical structures such as the underlying coronary conduits [9]. The target volumes should be defined according to the International Commission on Radiation Units and Measurements (ICRU) report 83 [19-21]. The clinical target volume (CTV) should encompass the tumor bed area, delineated by the surgical clips and any potential site of microscopic disease. Clips placed at the time of surgery denote the extent of resection in completely resected tumors and are useful in guiding postoperative irradiation. The planning target volume (PTV) must consider the margin of set up error covering inaccuracies of everyday positioning (Set-up) and those derived from the internal organs movement. High-energy (>10 MV) x-rays are preferred for RT and CT scan is necessary for adequate treatment planning. Respiratory movement is a major problem and the position of the tumor within the thorax can change the PTV margins. The more peripheral tumors are likely to move more with respiration than adjacent to or invading the mediastinal tumors. If a fourdimensional treatment-planning CT (4D-CT) is used, internal target volume (ITV) can be determined, which accounts for tumor motion. In 4D-CT it is possible to plan for RT-coordinated breathing control, wherein the patient is treated only during a particular phase of the breathing cycle. 4D-CT allows better sparing of normal critical structures like vessels and graft. The contouring of the heart will be along with the pericardial sac. The base will begin at the level of the inferior aspect of the pulmonary artery passing the midline and extend inferiorly to the heart's apex [22]. The great vessels should be delineated using mediastinal CT windowing to correspond to the vascular wall and all muscular layers out to the fatty adventitia (5 mm from the contrast enhanced vascular wall). The great vessels should be contoured starting at least 3 cm above the PTV's superior extent and continuing to at least 3 cm below the PTV's inferior extent. PET/CT helps distinguish tumor from mediastinal structures or collapsed lung and decreases the interobserver and intraobserver variability in target delineation.

Conclusions

Chronic radiation vasculopathy from RT is characterized by increasing rates of hemodynamically significant stenosis with time. Disease expression is the consequence of the combined radiation lesion to the intima media (endothelium) and the vasa vasorum (adventitia). Occlusion of the existing grafts may occur which could affect the survival of the patient while the benefits from RT are not well established. Further studies should ensue to compare the RT resistance of saphenous vein and various types of arterial grafts. The administration of RT in a patient with R0 stage II thymoma and prior coronary surgery is not advisable. RT is shown to be associated with better OS for stage IIB to III disease and positive margins but there is no evidence from randomized studies [23].

Conflict of interests

The authors declare no conflict of interests.

References

1. Proceedings of the First International Conference on Thymic Malignancies. August 20-21, 2009. Bethesda, Maryland, USA. J Thorac Oncol 2010;5(10 Suppl 4):259-370.
2. Engels EA. Epidemiology of thymoma and associated malignancies. J Thorac Oncol 2010;5(10 Suppl 4): 260-5.
3. Masaoka A. Staging system of thymoma. J Thorac Oncol 2010;5(10 Suppl 4):S304-12.
4. Blumberg D, Port JL, Weksler B et al. Thymoma: a multivariate analysis of factors predicting survival. Ann Thorac Surg 1995;8:908-13.
5. Curran WJ Jr, Kornstein MJ, Brooks JJ et al. Invasive thymoma: the role of mediastinal irradiation following complete or incomplete surgical resection. J Clin Oncol 1988;8:1722-7.
6. Ciernik IF, Meier U, Lutolf UM. Prognostic factors and outcome of incompletely resected invasive thymoma following radiation therapy. J Clin Oncol 1994;8:148490.

7. Chen YD, Feng QF, Lu HZ et al. Role of adjuvant radiotherapy for stage II thymoma after complete tumor resection. Int J Radiat Oncol Biol Phys 2010;8:14006.
8. Fan C, Feng Q, Chen Y et al. Postoperative radiotherapy for completely resected Masaoka stage III thymoma: a retrospective study of 65 cases from a single institution. Radiat Oncol 2013;8:199.
9. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Thymomas and Thymic Carcinomas. Available at: http://www.nccn.org/professionals/physician_gls/PDF/thymic.pdf.
10. Gujral DM, Shah BN, Chahal NS et al. Clinical Features of Radiation-induced Carotid Atherosclerosis. Clin Oncol (R Coll Radiol) 2013: S0936-6555(13)00400-7.
11. Cheng SW, Ting AC, Wu LL. Ultrasonic analysis of plaque characteristics and intimal-medial thickness in radiation-induced atherosclerotic carotid arteries. Eur J Vasc Endovasc Surg 2002;24:499-504.
12. Fokkema M, den Hartog AG, Bots ML et al. Stenting versus surgery in patients with carotid stenosis after previous cervical radiation therapy: systematic review and meta-analysis. Stroke 2012;43:793-801.
13. Rengan R, Bonner Millar LP, Thomas CR. Uncommon Thoracic Tumors. Thymic Tumors. In: Gunderson L, Tepper J (Eds): Clinical Radiation Oncology (3rd Edn). Philadelphia: Elsevier-Saunders, 2012, pp 860-72.
14. Korst RJ, Kansler AL, Christos PJ et al. Adjuvant radiotherapy for thymic epithelial tumors: a systematic review and meta-analysis. Ann Thorac Surg 2009;87:1641-7.
15. Gomez D, Komaki R, Yu J et al. Radiation therapy definitions and reporting guidelines for thymic malignancies. J Thorac Oncol 2011;6 (7 Suppl 3):1743-8.
16. Singhal S, Shrager JB, Rosenthal DI et al. Comparison of stages I-II thymoma treated by complete resection with or without adjuvant radiation. Ann Thorac Surg 2003;76:1635-41; discussion 1641-2.
17. Rena O, Papalia E, Oliaro A et al. Does adjuvant radiation therapy improve disease-free survival in completely resected Masaoka stage II thymoma? Eur J Cardiothorac Surg 2007;31:109-13.
18. Mangi AA, Wright CD, Allan JS et al. Adjuvant radiation therapy for stage II thymoma. Ann Thorac Surg 2002;74:1033-7.
19. IMRT Documentation Working Group, Holmes T, Das R, Low D et al. American Society of Radiation Oncology recommendations for documenting intensity-modulated radiation therapy treatments. Int J Radiat Oncol Biol Phys 2009;74:1311-8.
20. ICRU Report 83: Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT). Journal of the ICRU 2010;10. Available at: http://jicru.oxfordjournals.org/content/10/1.toc.
21. Grégoire V, Mackie TR. State of the art on dose prescription, reporting and recording in Intensity-Modulated Radiation Therapy (ICRU report No. 83). Cancer Radiother 2011;15:555-9.
22. Kong FM, Ritter T, Quint DJ et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. Int J Radiat Oncol Biol Phys 2011;81:1442-57.
23. Jackson MW, Palma DA, Camidge DR et al. The Impact of Postoperative Radiotherapy for Thymoma and Thymic Carcinoma. J Thorac Oncol 2017;12:734-44.