Radiotherapy in Thymic Tumors

16

Ugur Selek, Yasemin Bolukbasi, Erkan Topkan, and Ritsuko Komaki

Pathological and Biological Features

The thymus normally has separate lobules, with a sharp distinction between the lymphocyte-rich cortex and the epithelial cell-rich medulla which also contains characteristic Hassall's corpuscles of concentric layers of mature epithelial cells [5]. Thymic neoplasms arising in the anterior mediastinum are rare, but, variations in migration of embryonic endodermal epithelium of the third pharyngeal pouches could account for findings of gross or microscopic thymic tissue anywhere between the hyoid bone and the diaphragm [6]. The thymus, primarily involved in the processing and maturation of lymphocytes to be released into circulation as T lymphocytes, is very small at birth (approximately 15 g), grows to 40–45 g around puberty, and continuously involutes in elderly to an atrophic state.

U. Selek, MD
Department of Radiation Oncology, Koc University, Faculty of Medicine, Istanbul, Turkey

Department of Radiation Oncology, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA

Y. Bolukbasi
Department of Radiation Oncology, Koc University, Faculty of Medicine, Istanbul, Turkey

E. Topkan, MD
Department of Radiation Oncology, Baskent University, Adana, Turkey

R. Komaki, MD (✉)
Division of Radiation Oncology, The University of Texas, MD Anderson Cancer Center, 1515 Holcombe Blvd, B2.4451, Unit 97, Houston, TX, USA
e-mail: rkomaki@mdanderson.org

G. Ozyigit et al. (eds.), *Principles and Practice of Radiotherapy Techniques in Thoracic Malignancies*, DOI 10.1007/978-3-319-28761-4_16

Pathology

The World Health Organization (WHO) histological classification system for thymoma was announced in 1999 [7], and it has been shown to be reproducible for clinically distinct patient groups and have independent prognostic value for clinical management decisions [8]. The subgroups of primary epithelial thymic tumors, types A, AB, B1, B2, B3, and C (thymic carcinoma), are given in Table 16.1, accompanied with common terminology [9]. WHO type A and AB are generally encapsulated and clinically associated with stage I or II disease, whereas other histologies are frequently associated with invasive and disseminated disease (stage III or IV) [8, 10].

Staging

A workup revealing a well-defined anterior mediastinal mass in the thymic bed, with negative tumor markers and absence of continuity with the thyroid, indicates a thymic tumor and mandates multidisciplinary evaluation for tissue diagnosis and resectability (Table 16.2). The most often recommended imaging modality the

Table 16.1 The subgroups of primary epithelial thymic tumors

Epithelial thymoma type	Terminology	Frequency (%)	Composed of
A	Spindle cell; medullary thymoma	9	Few lymphocytes and bland spindle cells
AB	Mixed thymoma	24	Resembling type A plus predominant lymphocytic infiltrate and plump cells
B1	Predominantly cortical; organoid; lymphocytic; lymphocyte-rich thymoma	13	Predominant lymphocytic population and epithelial cells with vesicular and small nucleoli
B2	Cortical thymoma	24	Predominantly lymphocytic thymoma with scattered plump cells with vesicular nuclei
B3	Well-differentiated thymic carcinoma; epithelial; squamoid; atypical thymoma	15	Predominantly polygonal or round epithelial cells with mild atypia
C	Thymic carcinoma	15	Highly atypical cells which do not resemble the thymic organ and lack the immature T-cell lymphocytes: epidermoid keratinizing (squamous cell); epidermoid non-keratinizing; lymphoepithelioma-like; sarcomatoid; clear cell; basaloid; *mucoepidermoid*; papillary; undifferentiated carcinoma

Table 16.2 Workup at initial evaluation

Workup		
Physical examination for adenopathy		
Complete blood count		
Comprehensive blood chemistry (including serum beta-human chorionic gonadotropin and alpha-fetoprotein to rule out germ cell tumors)		
Chest CT with IV contrast detailed based on ITMIG-modified RECIST criteria [11, 15]	Overall tumor burden	Five lesions (two per organ)
	Target lesion measurement plane	Axial
	Target lesion axis to be measured	Long axis (except pleura and lymph nodes)
	Lymph node: measurement plane	Short axis
	Lymph node: minimum size to be included as target lesion	15 mm
	Pleura: measurement plane	Short axis
	Pleura considered as one organ: number of lesions allowed	Unidimensional measurement composed of six lesions: two sites at three different levels
MRI of the chest if pericardial or great vessel invasion		
Pulmonary function tests		
PET-CT, optional		

staging workup is computerized tomography (CT) because it is the most reproducible method to measure lesions at admission and at follow-up for response assessment [11]. A CT-controlled core biopsy is generally the first step to highlight the histology and differential diagnosis, especially between lymphomas, lung cancers, germ cell tumors, and soft tissue sarcomas [4]. A recent meta-analysis of the use of ^{18}F-FDG-PET-CT for predicting WHO grade of malignancy in thymic epithelial tumors (TETs) compared maximum standardized uptake values (SUVmax) in patients with low-risk thymomas (A, AB, B1), high-risk thymomas (B2, B3), and thymic carcinomas (C) and demonstrated a statistically significant difference that could appropriately predict the malignant nature of the different TETs [12]. Tumor size and imaging features on CT were shown to distinguish between stage I–II and III–IV to possibly identify candidates for surgery [13, 14].

As no official and scientifically validated stage classification system has been established for thymic malignancies, the Masaoka system with the modification proposed by Koga et al. was selected by the International Thymic Malignancy Interest Group (ITMIG) to be used until 2017; clinical staging of thymic epithelial tumors is described in Table 16.3 [16–19].

Evidence-Based Treatment Approaches

As the extent of malignancy is generally defined by microscopic or macroscopic invasion of the tumor capsule or surrounding organs, exploration at surgery is critical for establishing the malignant nature of a thymoma. Surgical series emphasize the

Table 16.3 Masaoka system, proposed modification of Koga, and Yamakawa-Masaoka TNM staging [10, 16, 17, 19]

Masaoka's clinical staging [16]			
Stage I: macroscopically completely encapsulated and microscopically no capsular invasion			
Stage II: macroscopic invasion into surrounding fatty tissue or mediastinal pleura or microscopic invasion into capsule			
Stage III: Macroscopic invasion into neighboring organs, i.e., pericardium, great vessels, or the lung			
Stage IVa: pleural or pericardial dissemination			
Stage IVb: lymphogenous or hematogenous metastasis			
Proposed modification of Koga's pathologic tumor extent [10, 17]			
Stage I: grossly and microscopically completely encapsulated			
Stage II: microscopic transcapsular invasion (IIa) or macroscopic invasion into thymic or surrounding fatty tissue or grossly adherent to but not breaking through mediastinal pleura or pericardium (IIb)			
Stage III: macroscopic invasion of neighboring organ (e.g., pericardium, great vessels, or the lung)			
Stage IVa: pleural or pericardial dissemination			
Stage IVb: lymphogenous or hematogenous metastasis			
Yamakawa-Masaoka TNM classification and staging [19]			
T factor			
T1: macroscopically completely encapsulated and microscopically no capsular invasion			
T2: macroscopically adhesion or invasion into surrounding fatty tissue or mediastinal pleura or microscopic invasion into capsule			
T3: invasion into neighboring organs, such as pericardium, great vessels, and the lung			
T4: pleural or pericardial dissemination			
N factor			
N0: no lymph node metastasis			
N1: metastasis to anterior mediastinal lymph nodes			
N2: metastasis to intrathoracic lymph nodes except anterior mediastinal lymph nodes			
N3: metastasis to extrathoracic lymph nodes			
M factor			
M0: mo hematogenous metastasis			
M1: hematogenous metastasis			
TNM stage			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IVa	T4	N0	M0
Stage IVb	Any T	N1, 2, 3	M0
	Any T	Any N	M1

importance of en bloc and total resection of all invaded structures for significant disease-free and overall survival benefits in comparison to partial resection or biopsy alone, and the requirement of radiotherapy if complete resection it cannot be ensured [4, 20, 21]. The ITMIG also underlined the importance of en bloc complete resection

in both open and minimally invasive resection procedures and suggests considering all thymomas potentially malignant because even stage I thymomas could recur if not resected according to surgical oncologic principles. Resection must also include the surrounding thymus and fatty tissue (not shelled out) in addition to parietal and visceral metastases in case of invasion into the pleural space [22]. Therefore, the main treatment of early- stage disease is surgery, but unresectable and advanced disease requires a multimodality approach.

The prognosis is directly related to WHO histological classification type, Masaoka clinical stage, and surgical resection status [10, 16, 21, 23–25]. The role of radiotherapy should be considered in light of these factors.

Stage I

A stage I thymoma is understood to have no transcapsular invasion [10]. Masaoka stage I disease with complete resection provides 100 % survival rates at 5 years, and radiotherapy has no role in treatment because of the low likelihood of recurrence [23, 26–28]. The only randomized trial of stage I disease had 29 patients and demonstrated that postoperative radiotherapy (PORT) is not necessary for Masaoka stage I [28]; overall survival rates at 10 years were 92 % for surgery alone and 82 % for PORT. The Surveillance, Epidemiology, and End Results (SEER) registry data from 1973 to 2005 identified 275 Masaoka stage I patients and revealed no benefit from PORT and a possible adverse effect on 5-year cancer-specific survival rates (91 % vs. 98 %, $p=0.03$) [23].

Stage II

A tumor with transcapsular invasion (IIa), or macroscopic invasion into thymic or surrounding fatty tissue, or gross adherence to but not breaking through mediastinal pleura or pericardium (IIb), is designated stage II [10]. Though surgery-alone series with complete R0 resection noted a 98 % survival rate at 5 years, retrospective series have shown supportive [26, 29–31] or contrary [32–35] findings from the use of adjuvant radiotherapy for aggressive tumor histologies or Masaoka stage II disease. In cases of R0 resection with no residual disease on imaging, a multidisciplinary evaluation is necessary to define the risk and need for adjuvant treatment. The most important factors for recommending postoperative adjuvant radiotherapy should be positive surgical margins (R1 or R2 resection) or histological B-C, with high recurrence risk as opposed to R0 resection or and low risk for type A or AB [34, 36].

Stage III–IV

Stage III disease is based on microscopic findings and evidence of macroscopic invasion into neighboring organ, either partially or penetrating (e.g., mediastinal

pleura, pericardium, great vessel, or lung) [10]. Any pleural or pericardial tumor nodules separated from the primary tumor denote stage IVa, and involvement and hematogenous metastases denote stage IVb.

Preoperative radiological findings usually predict surgical resectability of thymoma; incomplete resections were found to be associated with ≥50 % abutment of an adjacent vessel and pleural nodularity as well as lobulated tumor contour, thoracic lymphadenopathy, and adjacent lung changes [14]. The length of contact between the tumor contour and the lung has been also considered a prognostic factor for pleural recurrence after surgery alone [37]. In general, locally advanced and bulky disease at preoperative staging justifies a neoadjuvant approach in an attempt to downstage disease before surgery, usually with cisplatin-based chemotherapy or less often with chemoradiotherapy [38, 39]. Locally invasive or unresectable thymoma or thymic carcinoma can be converted to resectable thymoma and thymic carcinoma with neoadjuvant chemotherapy consisting of cyclophosphamide, doxorubicin, cisplatin, and prednisone (CAPP) ×3 cycles, which has improved outcomes in a phase II study [40]. Patients all underwent thymectomy followed by PORT to the tumor bed to 50 Gy in 25 fractions and or to 60 Gy in 30 fractions if the microscopic margin was positive [40].

No consensus has been reached on the role and timing of radiotherapy for locally advanced disease. Kondo and Monden documented outcomes of 1320 patients with TET treated between 1990 and 1994 at 115 institutions and suggested that adjuvant radiotherapy could not effectively prevent local recurrences in Japanese patients with totally resected stage II or III Japanese patients; also, adjuvant radiation or chemotherapy did not improve the prognosis for patients with totally resected stage III–IV thymoma or thymic carcinoma [34]. In contrast, Curran et al. emphasized the importance of adjuvant radiotherapy for totally resected stage II or III disease; revealed mediastinal recurrence as the first site of failure in such cases after complete resection without radiotherapy, in addition to poor salvage; and noted a 5-year actuarial mediastinal relapse rate of 53 % after total resection without adjuvant radiotherapy, 0 % with radiotherapy, and 21 % after subtotal resection/biopsy plus radiotherapy [26]. Urgesi et al., reporting an experience with 59 stage III patients, also encouraged adjuvant radiotherapy [30]. SEER data suggested significant improvement with PORT for patients with Masaoka stage II–III disease, with at 5-year overall survival rates (76 % with PORT vs. 66 % for surgery alone, $p=0.01$) but not in cancer-specific survival at 5 years (91 % vs. 86 %, $p=0.12$); also, no benefit from PORT was found after extirpative surgery (defined as radical or total thymectomy) [23]. The conclusion of that study was that PORT had a possible benefit in overall survival in patients with Masaoka stage II–III disease, especially without R0 surgery. The Japanese Association for Research on the Thymus published their experience with 1110 Masaoka stage II or III thymoma cases and revealed no benefit from PORT on relapse-free or overall survival in these patients [41]. For stage III disease, PORT after even an R0 resection is usually recommended as adjuvant treatment regardless of histological type because the risk of local recurrence is high for this stage [42].

Thymic Carcinoma

Thymic carcinomas, with their aggressive clinical nature and poor prognosis, are distinct from the rest of the TETs [43].

The Japanese Association for Research on the Thymus recently emphasized the importance of PORT in a review of 155 stage II and III thymic carcinoma cases, as it improves relapse-free survival (hazard ratio, 0.48; 95 % confidence interval, 0.30–0.78; $p = 0.003$) but not overall survival, because patients with thymic carcinoma died of distant metastasis [41]. Another study of 1042 cases of thymic carcinoma also underlined the importance of PORT for an overall survival benefit [44]. The European Society of Thoracic Surgeons, reviewing 229 thymic carcinoma cases, found that PORT significantly prolonged overall survival [45]. Multimodality treatment is essential for prolonging survival. Molecular pathology of thymic carcinoma has been well documents; abnormalities of oncogenes and tumor suppressor genes in thymic carcinoma have led to significantly higher expression of EGFR, c-Kit, BCL2, and TP53 relative to thymoma [46]. Based on the clinical patterns of failures and the molecular pathology of thymoma versus thymic carcinoma, thymic carcinoma requires more aggressive systemic treatment, with PORT if the tumor is operable or aggressive chemoradiotherapy if it is not operable.

Target Volume Determination and Delineation Guidelines

The ITMIG initiative on radiation therapy definitions and reporting guidelines for radiation therapy for thymic malignancies has had greatly beneficial effects on documentation and global reproducibility (Table 16.4) [47].

Simulation

The simulation procedure for thymic tumors is similar to that for lung cancer, including the use of comfortable but strict immobilization for supine patients with their arms over their head (moving arms away from any possible beam angles), holding a T-bar if possible, and with the neck slightly extended, supported by a custom-made cushion for stability. The simulation CT images should preferably be in $\leq$3 mm slices; intravenous contrast is favored for better anatomical differentiation. A four-dimensional (4D) CT scan is preferred, if available to appropriately assess breathing-related internal motion during treatment planning [47, 48]; other motion-encompassing options could be slow CT scanning covering the whole breathing cycle or obtaining CT both at inspiratory and expiratory phases to define internal motion [49]. PET-CT can also be a good aid for tumor delineation.

Table 16.4 Short summary of technique-specific coverage and treatment planning details

Tumor GTV	iGTV/GTV to CTV margin	ITV/CTV to PTV margin	Neoadjuvant dose	Adjuvant dose		Definitive dose
				R0	R1–2	
The gross disease and any macroscopic invasion into thymic or surrounding fatty tissue or surrounding organs (mediastinal pleura, pericardium, great vessels, lung, etc.) plus any grossly involved lymph nodes (>1 cm or nodes with a necrotic center or PET positive)	0.5–1 cm craniocaudally and circumferentially	No 4DCT/motion management and daily IGRT: 1–1.5 cm	40–64 Gy in 1.8–2.0 Gy/fraction	45–50 Gy in 1.8–2.0 Gy/fraction	54–64 Gy in 1.8–2.0 Gy/fraction	54–70 Gy in 1.8–2.0 Gy/fraction
	Make sure to cover postoperative bed including surgical clips	4DCT/motion management or daily IGRT: 0.5–1 cm				
		Both 4DCT/motion management and daily IGRT: 0.5 cm				

IGRT, image-guided radiation therapy

Gross Tumor Volume

An appropriate GTV should include the gross disease and any macroscopic invasion into thymic or surrounding fatty tissue or surrounding organs (mediastinal pleura, pericardium, great vessels, lung, etc.) plus any grossly involved lymph nodes (nodes that are >1 cm in diameter or have a necrotic center or are positive on PET) which should be delineated on determined from CT, MRI, or PET-CT scans. A joint ITMIG radiologist/radiation oncologist task force is working on a consensus atlas for delineation recommendations but this atlas has yet to be completed.

Internal Target Volume or Internal GTV

The GTV contouring is based on 4D CT data (respiratory data sets are "binned" by phase: 0–100 % at 10 % intervals) in addition to all previously gathered information, and the iGTV is contoured by using the maximum intensity projection (MIP) settings, with modifications based on visual verification of contours in individual respiratory phases.

The GTV can be subdivided into the primary [tumor] site (GTV-P) and involved gross lymph nodes (GTV-N). Thorough contouring of the GTV-P is required based on the exact pattern of spread:

Radial and Local

- Is there mediastinal pleural invasion (T2)?
- Is there pericardium invasion (T3)?
- Is there lung invasion (T3)?
- Is there great vessels/heart invasion (T3)?
- Is there any pleural or pericardial nodule (T4)?

Nodal

- Is there nodal disease in anterior mediastinum (N1)?
- Is there intrathoracic nodal disease aside from anterior mediastinum (N2)?
- Is there extrathoracic nodal disease (N3)?

Clinical Target Volume (CTV)

CTV is delineated as any possible microscopic spread and areas at risk for microscopic spread in addition to the iGTV of the primary tumor and involved nodes, plus the preoperative extent and operative bed if surgery has been done (Figs. 16.1 and 16.2). The previous approach was to cover the whole mediastinum, but the current recommendation, in the era of CT simulation, is to limit the CTV by using preoperative imaging and intraoperative findings and surgical clips. The margin over the iGTV is 0.5–1.0 cm.

Planning Target Volume (PTV)

The PTV includes an extra margin around the CTV to compensate for variability and uncertainties in treatment setup (internal organ motion is handled with 4DCT or alternatives). Margins over the CTV are established in accordance with the

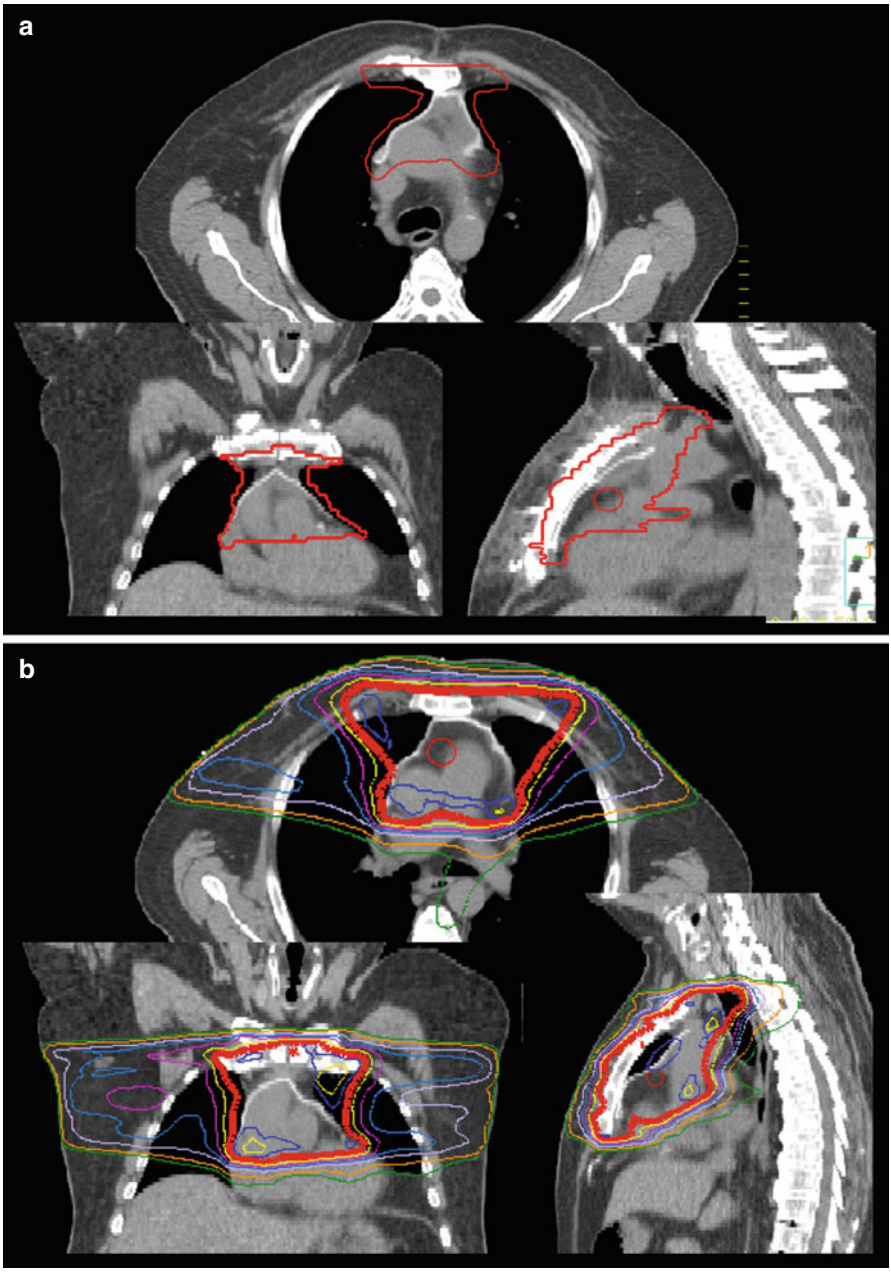

Fig. 16.1 A 57-year-old man with a 6-cm mass in the anterior mediastinum underwent surgery, and the mass invading the pericardium was resected with clear margins (Masaoka stage III, R0 resection, WHO type 2). The clinical target volume (CTV) was defined and 54 Gy (2 Gy/fraction/day) was prescribed to cover the preoperative mass, operative area, and the mesh graft after pericardial resection. Axial, coronal, and sagittal images are shown for delineation (**a**) and for dose distribution (**b**)

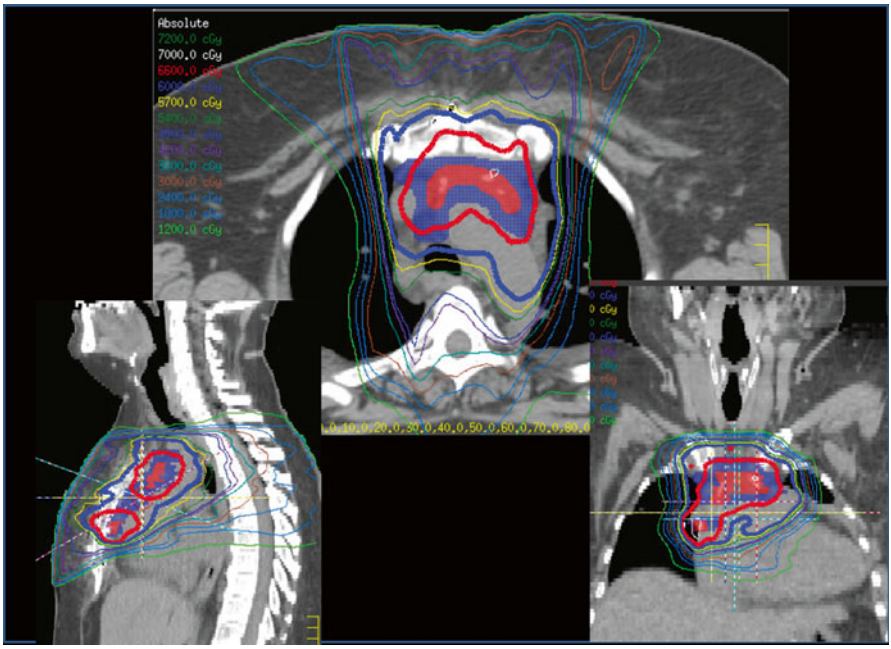

Fig. 16.2 A 59-year-old woman with an invasive mass located in the anterior mediastinum underwent biopsy revealing type B3 thymoma. She underwent four cycles of neoadjuvant chemotherapy (cisplatin, etoposide, ifosfamide) and then surgery with R2 resection. Radiation was prescribed as a simultaneous integrated boost with 59.4 Gy (1.8 Gy/fraction/day) covering the operative bed and 66 Gy (2 Gy/fraction/day) covering the grossly positive surgical margin; axial, coronal, and sagittal images are shown

techniques used for simulation (encompassing internal motion or not), and use of daily image guidance (kV, cone beam CT, etc.). Using advanced modalities could allow some margins to be reduced. If the treating institution has not defined the appropriate magnitude of the PTV, a minimum of 5 mm in all directions should be used for each PTV. Acceptable margins for CTV to PTV are as follows:

- −1.5 cm if without 4D CT or alternative simulation and without daily imaging
- 0.5–1.0 cm if with 4D CT or alternative simulation and without daily imaging
- 0.5 cm if both with 4D CT or alternative simulation and daily imaging

Case Contouring: A Case Example

A 47-year-old woman with a 5-cm mass located in the anterior mediastinum underwent surgery, and the mass invading the pericardium was resected with clear margins (Masaoka stage III disease, R0 resection, WHO type 2). The CTV was defined and 54 Gy (1.8 Gy/fraction/day) was prescribed to cover the preoperative mass and operative area; axial slice-by-slice images used for CTV delineation are shown in Fig. 16.3.

Treatment Planning

No randomized trial data exist to support the choice of radiotherapy doses for thymoma and thymic carcinoma but a general consensus comes from the studies shown in Table 16.5 [42, 47]. Kundel et al. reported that PORT to doses above 45 Gy improved disease-free and overall survival in their patients with invasive stage II thymoma [50]. Zhu et al. pointed out the prognostic importance of doses above 50 Gy for 5-year overall survival for patients with unresectable disease [51], and Fuller et al. underlined the significance of doses above 60 Gy for unresectable or local residual disease [24]. ITMIG guidelines outline the minimum postoperative adjuvant dose for patients with R0 resection for thymoma should be 40 Gy, in

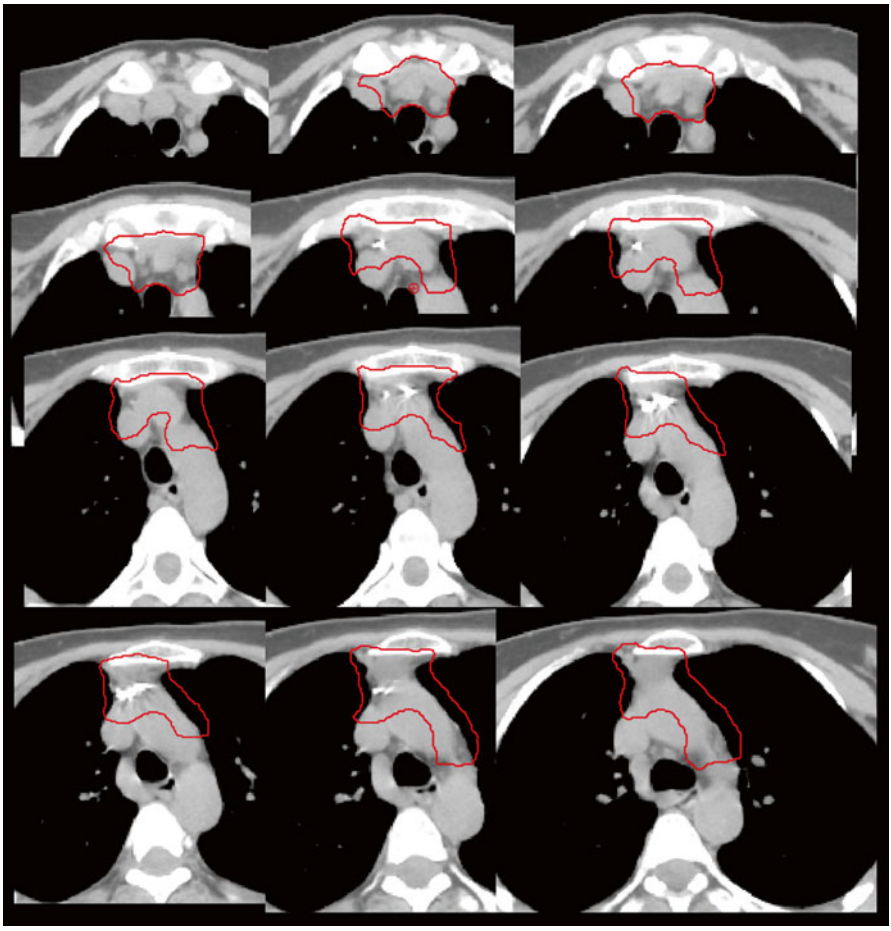

Fig. 16.3 A 47-year-old woman with a 5-cm mass located in the anterior mediastinum underwent surgery, and the mass invading the pericardium was resected with clear margins (Masaoka stage III, R0 resection, WHO type 2). The CTV was delineated and 54 Gy (1.8 Gy/fraction/day) prescribed to cover the preoperative mass and operative area. Shown are axial slice-by-slice images of tumor borders

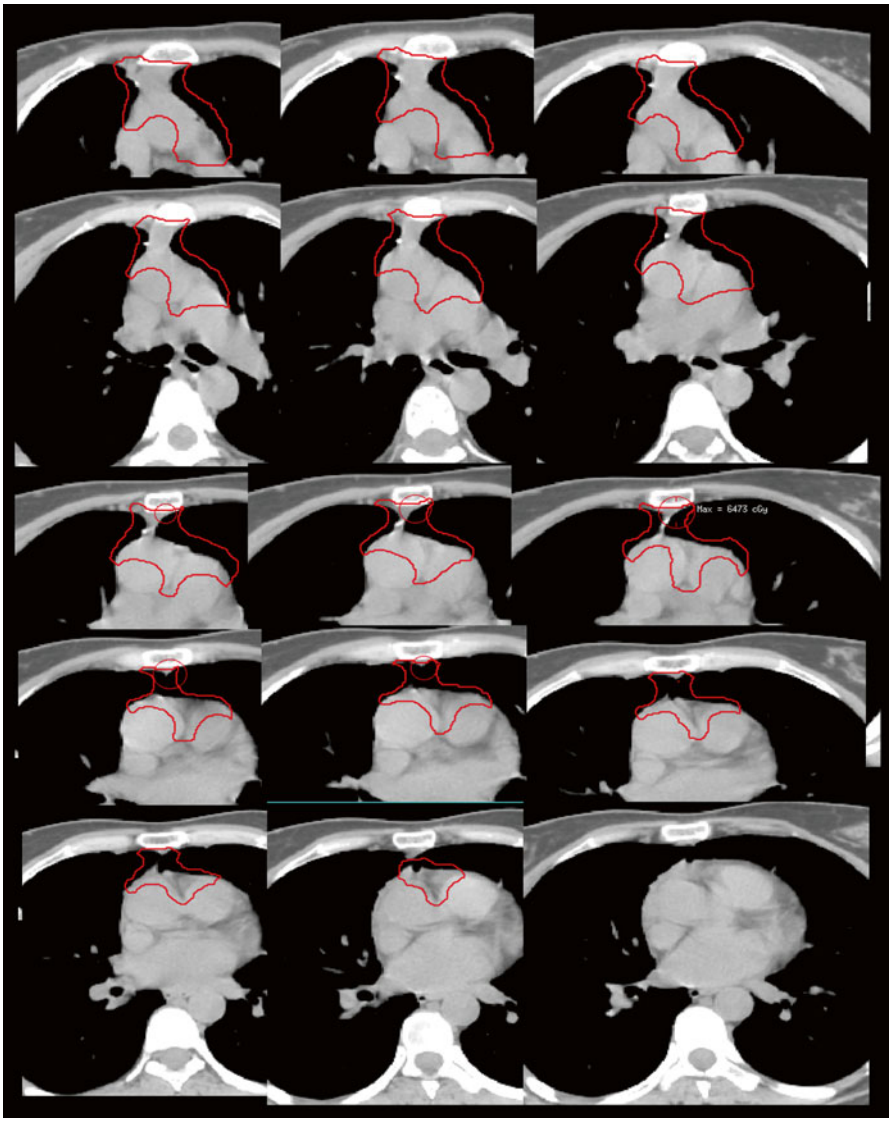

Fig. 16.3 (continued)

1.8–2 Gy fractions; doses below 54 Gy are not recommended for gross residual disease in case of R1/R2 resection; and doses above 64 Gy are not considered appropriate in the postoperative setting [47]. Because patients given PORT for invasive thymoma could live long enough to manifest late effects of cardiac toxicity such as coronary artery disease or myocardial infarcts, PORT needs to be given within dose volume constraints [47]. It is very important to use proton treatment – if available – to reduce cardiac dose in cases in which the treatment volume is very large [48] (Fig. 16.4).

Table 16.5 Summary of thymoma trials from different centers

Author, year	Center	#	Dose	5-year local control	5-year disease-free survival	5-year overall survival
Nakahara 1988 [52]	Osaka University	141	Postoperative 30 Gy in 3 weeks to 50 Gy in 6 weeks	–	–	100 %, stage I; 91.5 %, stage II; 87.8 %, stage III; 46.6 %, stage IV
Curran 1988 [26]	Fox Chase Cancer Center	103	Postoperative 32–60 Gy	100 % for R0 stage II and III; 79 % for R1–2 stage II and III	100 %, stage I; 58 %, stage II; 53 %, stage III	67 %, stage I; 86 %, stage II; 69 %, stage III
Urgesi 1990 [30]	University of Torino	77	Postoperative 39.6 and 46 Gy whole mediastinum plus 10–16 Gy boost. Preoperative 30 Gy followed by a postoperative boost of 16–24 Gy	–	–	70.9 %, stage III; 26.3 %, stage IVa
Jackson 1991 [53]	Peter MacCallum Cancer Institute	28	Postoperative 40–50 Gy	61 %	–	53 %
Haniuda 1992 [54, 55]	Shinshu University	70	Postoperative 40–50 Gy	100 %, stage I and stage II p0 with or without RT; 100 %, stage II p1 with RT and 63.6 % without RT	–	74 % for stage II
Pollack 1992 [56]	U. T. M. D. Anderson Cancer Center	36	Postoperative median dose 50 Gy (40–60)	–	4 %, stage I;71 %, stage II; 50 %, stage III; 29 %, stage IVA	74 %, stage I; 71 %,stage II; 50 %, stage III, 29 %, stage IV

Cowen 1995 [57]	10 French centers	149	Preoperative 22–50 Gy; postoperative 30–70 Gy	100 %, stage I; 98 %, stage II;69 %, stage III;59 % stage IVa	59.5 %	–
Mornex,1995 [29]	10 French cancer centers	90	Postoperative 30–70 Gy	66 %, stage III and IV; 84 %, after partial resection vs. 55 % after biopsy	–	51 %
Regnard 1996 [58]	Marie Lannelongue Hospital	307	Postoperative in invasive or metastatic cases	–	55 %, surgery; 59 PORT at 15 years	–
Latz 1997 [33]	University of Heidelberg	43	Postoperative 10–72 Gy	81 % within the radiation field	–	90 %,stage II; 67 %, stage III; 30 %, stage IV
Gripp 1998 [59]	Heinrich-Heine-University	70	Postoperative 45 (20–60) Gy	50 %, surgery; 80 %, PORT for R0	–	–
Myojin 2000 [60]	Massachusetts General Hospital	32	Preoperative 40 Gy; postoperative 45–50 Gy for close resection margins, 54 Gy for R1, and 60 Gy for R2	62.5 %	–	71 %
Mangi 2002 [32]	Massachusetts General Hospital	49 (stage II)	Postoperatively 45.5 (30–61) Gy	–	–	84 %, surgery; 100 %, PORT at 15 years
Kondo 2003 [34]	115 Japanese institutes	1320	Postoperatively 40 Gy	99.1 %, stage I; 95.9 %, stage II; 71.6 %, stage III; 65.7 %, stage IV	–	93 %, total resection; 64 %, subtotal resection; 36 %, inoperable for stage III and IV thymoma
Singhal 2003 [36]	Pennsylvania	70	Postoperatively 45–55 Gy	–	–	91 %

(continued)

Table 16.5 (continued)

Author, year	Center	#	Dose	5-year local control	5-year disease-free survival	5-year overall survival
Eralp 2003 [61]	University of Istanbul, Capa	36	Postoperatively 50.4–60 Gy	–	–	56.9 months, surgery; 106.3 months, PORT
Zhu 2004 [51]	Cancer Hospital of Fudan University	175	Postoperative 50–55 if R0, 60–65 if R1/R2	99.6 %, stage I; 56.4 %, stage II; 42.7 %, stage III; 21.6 %, stage IV	–	96 %, stage I; 77.8 %, stage II; 56.6 %, stage III; 35.6 % stage IV
Kim 2004 [40]	University of Texas, M. D. Anderson Cancer Center	22, trimodality	Postoperative 50 Gy if R0, 60 if R1	–	77 %	20/22 alive at analysis
Mangi 2005 [62]	Massachusetts General Hospital	45	–	–	–	Disease-specific survival at 5 years: 75 %, surgery; 79 %, PORT
Rena 2007 [63]	University of Eastern Piedmont "A. Avogadro"	58 stage II	Postoperative 50 (45–54) Gy	–	94 %	No difference
Utsumi 2009 [64]	Osaka University	324	Postoperative 10–50 Gy	–	92.8 % with RT; 94.4 % without RT. 10 years for patients without RT, Masaoka stage I and II, WHO A, AB, or B1, was 100 %	10 years, 77.3 % stage I, 85 % stage II, 79.9 % stage III, 62.5 % stage IV
Vasiliou 2009 [65]	University of Patras	41	Postoperative 50.7 (39–58) Gy	–	90.5 months, surgery; 43 months, PORT	–

Fernandes 2010	SEER	1334	–	–	–	PORT does not increase the risk of cardiac mortality or secondary malignancy
Forquer 2010 [23]	SEER	901	–	–	–	76 %, PORT; 66 %, surgery alone, Masaoka stage II and III (cancer-specific survival 91 % PORT; 86 %, surgery alone)
Chen 2010 [66]	Tianjin Medical University Cancer Hospital	142	Postoperative 60 (22–60) Gy	–	97.6 %, surgery; 92.3 %, PORT	Disease-specific survival at 5 years: 97.5 %, surgery; 96.4 %, PORT
Chang 2011 [67]	Seoul National University	76	Postoperative 50 Gy (range: 43.2–66 Gy)	The median time to recurrence; 37.4, surgery; 50.6 months, PORT	80 %, surgery; 97.8 %, PORT	–
Berman 2011 [68]	University of Pennsylvania	62	Postoperative 50.4 Gy (range:45–74.6 Gy)	Proportion of recurrences: 8 %, surgery; 0 %, PORT	–	One death occurred in each group, observation, and radiation
Oh 2012 [69]	Samsung Medical Center, Sungkyunkwan University	110, stage I–II	Postoperative 54 (44–60) Gy	–	98.1 %, surgery; 94.5 %, PORT at 10 years	Disease-specific survival: 100 %, surgery; 93.5 %, PORT at 10 years
Weksler 2012 [70]	SEER	476 stage III	Postoperatively	–	–	105 months, surgery; 127 months, PORT
Fan 2013 [71]	–	65 stage III	Postoperative 56 (28–60) Gy	–	–	81.5 %, surgery; 91.7 %, PORT

(continued)

Table 16.5 (continued)

Author, year	Center	#	Dose	5-year local control	5-year disease-free survival	5-year overall survival
Gao 2013 [72]	Chest Hospital of Jiao Tong University, Sixth Hospital of Jiao Tong University	105 type B3	Postoperative 49 (36–66) Gy	–	–	Masaoka stage and adjuvant radiation are prognostic factors for stage III and IV
Yan 2014 [73]	University of Washington Medical Center	40	Postoperative 50.4 (45–55) Gy for stage II; 59.4 (45–70) Gy for stage III	–	–	72.9 %, surgery; 88.4 %, PORT, potential OS benefit in positive margin
Song 2014 [74]	Zhejiang Cancer Hospital	42 type B2	Postoperative 40–60 Gy	–	62.8 %	84.9 %, PORT had no effect in type B2
Rathod 2014 [75]	Tata Memorial Hospital	62	50–60 Gy, radical; 39 Gy, palliative	–	–	90 % at 3 years. Resectable, 94 %; non-resectable, 81 %
Häfner 2015 [76]	Heidelberg University Hospital	41	Postoperative 51.7 (49–60) Gy	–	100 %, WHO A/AB/B1/B2; 63.6 %, B3/C	100 %, stages I + II; 80 %, stage III; 66.7 %, stage IV
Omasa 2015 [41]	32 Japanese institutions	155 thymic carcinoma and 1110 thymoma	–	–	PORT for stage II and III thymic carcinoma: hazard ratio, 0.48; $P=0.003$. PORT for stage II and III thymoma: not significant	For stage II and III thymic carcinoma: hazard ratio, 0.94; 95 %; $P=0.536$. PORT for stage II and III thymoma: not significant
Perri 2015 [77]	Italy	22	Postoperative 50 (range 44–60) Gy	68 %		74 %

PORT postoperative radiotherapy, *RT* radiotherapy, *SEER* the Surveillance, Epidemiology, and End Results registry data, *p0* no adhesion to the mediastinal pleura, *p1* fibrous adhesion to the mediastinal pleura without microscopic invasion, and *p2* microscopic invasion of the mediastinal pleura

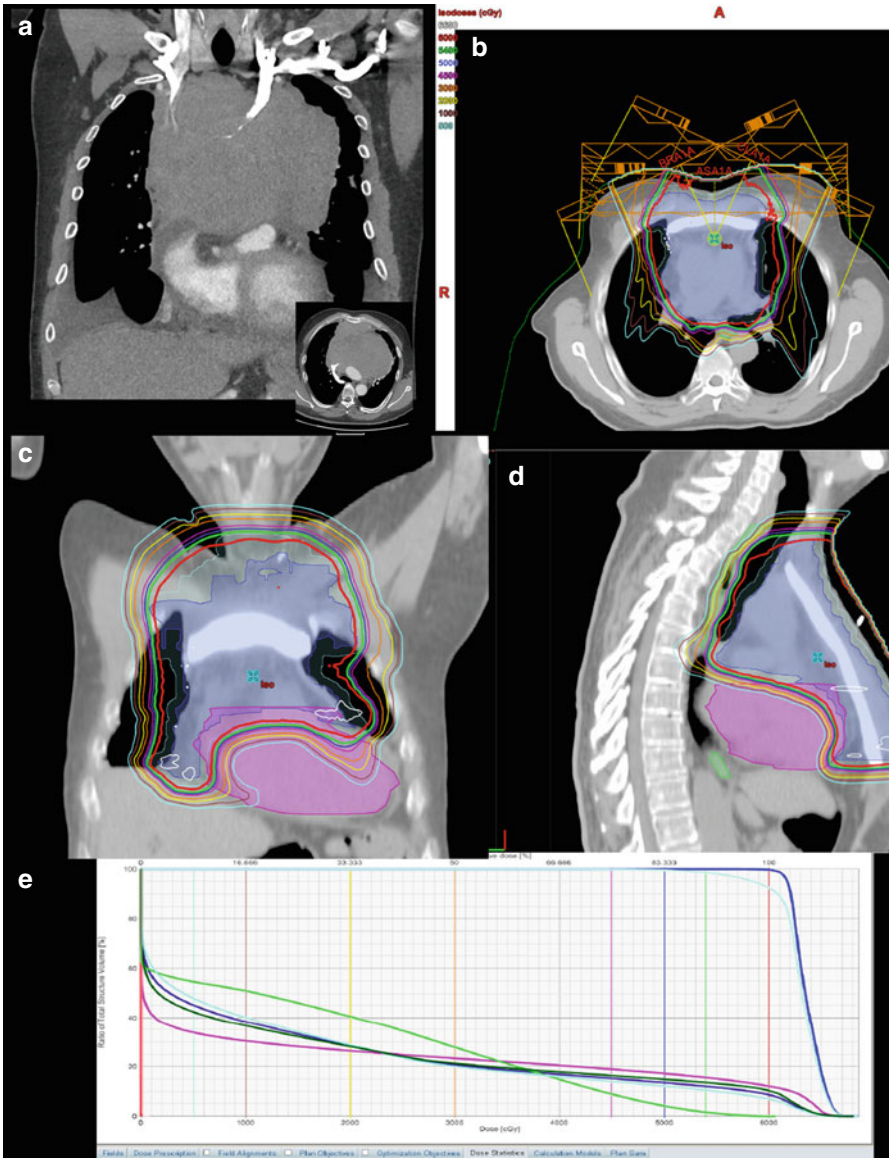

Fig. 16.4 A 51-year-old man with Masaoka stage IVA invasive thymoma. He underwent neoadjuvant chemotherapy consisting of 4 cycles of cyclophosphamide, doxorubicin vincristine, and cisplatin with minimal response. Because the tumor still measured 23 cm, a neoadjuvant radiotherapy approach was not possible, and he underwent second-line chemotherapy with gemcitabine, which he could not tolerate. (**a**) coronal and axial after chemotherapy. He then underwent a very extensive radical thymectomy with reconstruction of the sternum after resection of the medial portion of the 1st through 10th medial ribs bilaterally in addition to removal of the phrenic nerve and pericardium. Because of the positive margins were still evident after surgery, PORT, was prescribed with protons (60 Gy, in 30 fractions of 2 Gy/fraction/day). axial (**b**), coronal (**c**), sagittal (**d**), and dose volume histogram (**e**) images are shown

Guidelines for delineating organs at risk have been standardized in RTOG atlases [78]; normal tissue constraints can be based on quantitative analysis of normal tissue effects in the clinic (QUANTEC) guidelines with normal tissue complication probability models (Table 16.6) [47, 79].

Treatment Planning Assessment

Our institutional standard is to deliver 100 % prescribed dose to the GTV and 95 % of the prescribed dose to the PTV.

- Step 1: Check whether the targets are adequately covered: All plans should be normalized to cover at least 95 % of the volume of PTV by the prescribed isodose surface and 99 % of the PTV needs to be at or above 93 % of the prescribed dose.
- Step 2: Check whether a large hot spot: is present. No more than 20 % of the PTV is at or above 107 % of the prescribed dose, and no more than 5 % of the PTV is at or above 114 % of the prescribed dose.

Table 16.6 Guidelines for normal tissue constraints [47, 79]

Organ	Constraints		
Spinal cord	D_{max} <45 Gy		
	D_{max} <40 Gy if 3 Gy/fraction		
	Even the tumor too close, D_{max} should be <60 Gy		
Lung (total lung GTV; solely total lung for postoperative cases without GTV)	Mean dose < 20 Gy		
	Mean dose < 8 Gy if post-pneumonectomy		
	RT Alone	RT with concurrent chemotherapy	Neoadjuvant treatment before surgery
	V_{20} ≤40 %	V_{20} ≤35 %	V_{20} ≤30 %
		V_{10} ≤45 %	V_{10} ≤40 %
		V_5 ≤65 %	V_5 ≤55 %
	V20 <10 % and V5 <60 % if post-pneumonectomy		
Heart	Mean dose <26 Gy		
	V_{30} ≤45 %		
Esophagus	Mean dose <34 Gy		
	D_{max} ≤80 Gy		
	V_{70} <20 %		
	V_{50} <50 %		
Kidney	20 Gy <32 % of bilateral kidney		
Liver	Mean dose <30 Gy		
	V30 <40 %		

Dmax maximal dose, *GTV* gross tumor volume, *RT* radiotherapy

- Step 3: Check whether the normal tissue constraints are met.
- Step 4: Check whether the placement of the hot/cold spots is correct (slide by slide, by looking at isodose distribution): hot spots need to be located in the GTV.

Recommended Treatment Algorithm for Treatment of Thymoma

The recommended algorithm for the treatment of thymoma is summarized in Table 16.7.

Recommended Algorithm for Follow-Up

The recommended algorithm for follow-up is summarized in Fig. 16.5.

Table 16.7 Recommended treatment algorithm for treatment of thymoma

	Masaoka I		Masaoka II		Masaoka III		Masaoka IV
WHO pathology	R0	R1–2	R0	R1–2	R0	R1–2	R1–2
A, AB, B1	Ø	RT	Ø	RT	RT	RT	CRT
B2, B3, TC	Ø	RT	RT	CRT	RT/CRT	CRT	CRT

R0 complete resection, *R1–R2* microscopic/gross residual disease, *RT* postoperative radiotherapy, *CRT* concurrent or sequential chemotherapy and radiotherapy

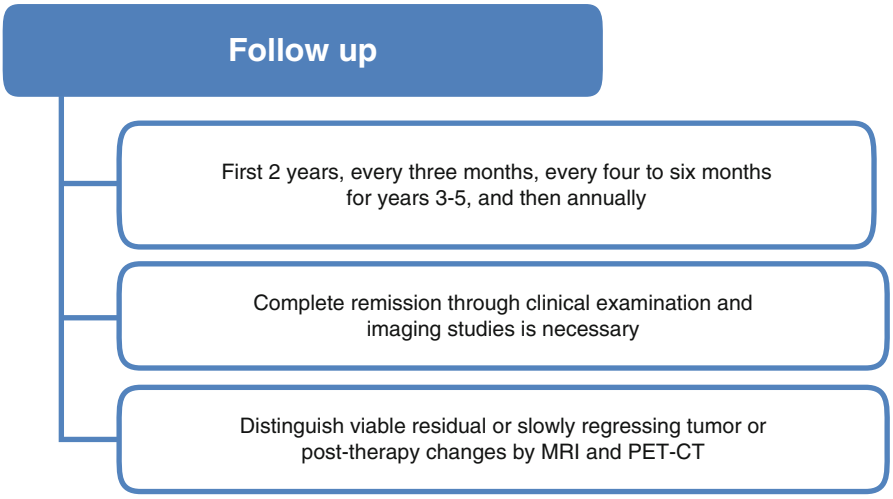

Fig. 16.5 Recommended algorithm for follow-up

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