RADIORYTHMIC: Phase III, Opened, Randomized Study of Postoperative Radiotherapy Versus Surveillance in Stage IIb/III of Masaoka Koga Thymoma after Complete Surgical Resection

C. Basse,[1,#] A. Botticella,[2,#] T.J. Molina,[3] P.E. Falcoz,[4] Y. Oulkhouir,[5] M. Kerjouan,[6] E. Pichon,[7] V. Westeel,[8] L. Thiberville,[9] X. Quantin,[10] C. Clément-Duchêne,[11] J. Khalifa,[12] F. Le Tinier,[13] M. Ginoux,[14] F. Thillays,[15] P. Mordant,[16] B. Besse,[17] P.A. Thomas,[18,##] C. Le Péchoux,[19,##] Nicolas Girard[20,##]

ABSTRACT

Introduction: Thymomas are rare intrathoracic malignancies that may be aggressive and difficult to treat. Knowledge and level of evidence for treatment strategies are mainly based on retrospective studies or expert opinion. Currently there is no strong evidence that postoperative radiotherapy after complete resection of localized thymoma is associated with survival benefit in patients. RADIORYTHMIC is a phase III, randomized trial aiming at comparing postoperative radiotherapy versus surveillance after complete resection of Masaoka-Koga stage IIb/III thymoma. Systematic central pathologic review will be performed before patient enrollment as per the RYTHMIC network pathway. **Patients and Methods:** Three hundred fourteen patients will be included; randomization 1:1 will attribute either postoperative radiotherapy (50-54 Gy to the mediastinum using intensity-modulated radiation therapy or proton beam therapy) or surveillance. Stratification criteria include histologic grading (thymoma type A, AB, B1 vs B2, B3), stage, and delivery of preoperative chemotherapy. Patient recruitment will be mainly made through the French RYTHMIC network of 15 expert centers participating in a nationwide multidisciplinary tumor board. Follow-up will last 7 years. The primary endpoint is recurrence-free survival. Secondary objectives include overall survival, assessment of acute and late toxicities, and analysis of prognostic and predictive biomarkers. **Results:** The first patient will be enrolled in January 2021, with results expected in 2028.

Clinical Lung Cancer, Vol. 22, No. 5, 469–472
Keywords: Thymoma, Postoperative radiotherapy, Surveillance, Network, Surgery

Introduction

Thymic epithelial tumors (TETs) are rare intrathoracic malignancies, which may be aggressive and difficult to treat. The number of new cases per year is estimated to range between 250 and 300 in France.[1,2] TETs are classified according to the World Health Organization histopathologic classification, which distin-

[1]Thorax Institute Curie Montsouris, Institut Curie, Paris, France
[2]Radiotherapy Department, Institut Gustave Roussy, Villejuif, France
[3]Service d'anatomie pathologique, Hôpital Universitaire Necker-Enfants-Malades, AP-HP-Centre, INSERM U1163, Institut Imagine, Université de Paris, Paris, France
[4]Thoracic Surgery Department, CHRU Strasbourg, Strasbourg, France
[5]Thoracic Oncology, CHU Caen, Caen, France
[6]Thoracic Oncology, CHU Rennes, Rennes, France
[7]Respiratory Medicine Department, CHU Tours, Tours, France
[8]Respiratory Medicine Department, CHRU Besançon, Besançon, France
[9]Respiratory Medicine Department, CHU Rouen, Rouen, France
[10]Institut de Cancérologie de Montpellier, Montpellier, France
[11]Oncology Department, Institut de Cancérologie de Lorraine, Nancy, France
[12]Radiotherapy Department, IUCT Oncopole Toulouse, Toulouse, France
[13]Radiotherapy Department, Centre Oscar Lambret, Lille, France
[14]Respiratory Medicine Department, Hospices Civils de Lyon, Lyon, France
[15]Radiotherapy Department, Institut de Cancérologie de l'Ouest, Nantes, France
[16]Thoracic Surgery Department, Hôpital Bichat, Paris, France
[17]Medical Oncology Department, Institut Gustave Roussy, Villejuif, France
[18]Thoracic Surgery Department, CHU Marseille, Marseille, France
[19]Radiotherapy department, Institut Gustave Roussy, Villejuif, Villejuif, France
[20]Thoracic Oncology, Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France

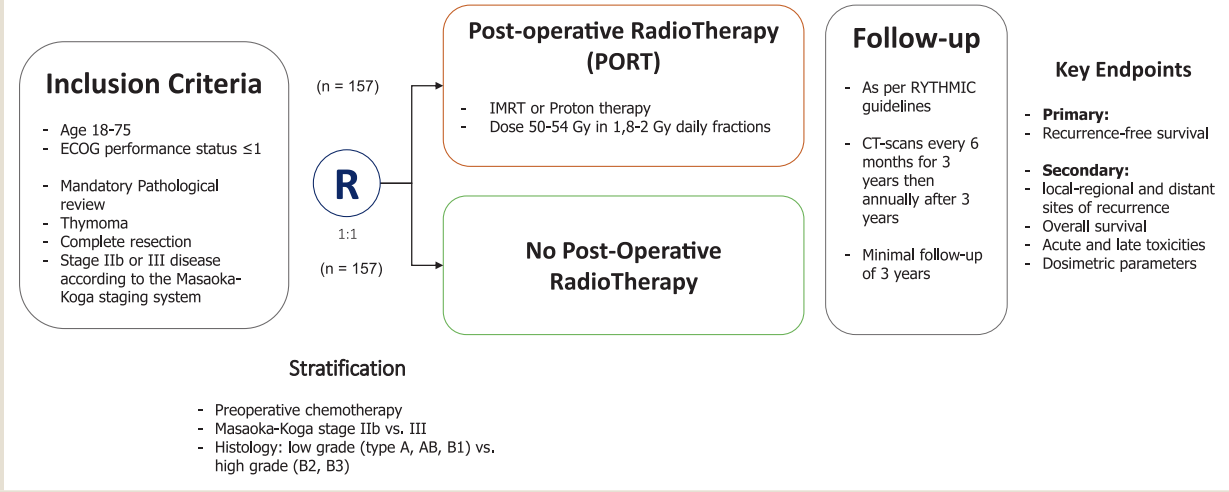
Submitted: Dec 17, 2020; Accepted: Jan 26, 2021

Address for correspondence: Nicholas Girard, Institut Curie, Thorax Institute, 26 rue d'Ulm, 75005 Paris, France.
E-mail contact: nicolas.girard2@curie.fr

[#] C.B. and A.B. contributed equally to this work as first authors.
[##] P.A.T., C.L.P., and N.G. contributed equally to this work as last authors.

1525-7304/$ - see front matter
https://doi.org/10.1016/j.cllc.2021.01.020

Figure 1 Study design.



guishes thymomas from thymic carcinomas.[1] Thymomas are more frequent than carcinomas, and are further divided into 5 subtypes (A, AB, B1, B2, and B3). TETs are historically staged according to the Masaoka-Koga staging system,[1] which has been replaced by the eighth TNM staging classification.[1–5] The treatment strategy for TETs primarily relies on the surgical resection of the tumor, which represents the most significant prognostic factor on survival, and is proposed to 70% of patients.[1] Preoperative, primary chemotherapy may be proposed when complete resection is deemed not to be achievable upfront.[1,2]

A major challenge in TETs is the occurrence of recurrences after surgery, which may be observed in 10% to 70% of patients depending on histology, initial extent of the lesions as assessed by tumor stage, and completion of resection.[3,4] After complete resection of the tumor, stage remains the strongest predictor of recurrence, although the weight of histology remains uncertain. Recurrences may occur in up to 10% of cases in Masaoka-Koga stage I, 30% of cases in stage II thymomas, and 40% of cases in stage III thymomas; thymic carcinomas are associated with an even higher risk of recurrence, ranging from 50% to 90%.[1,2] Given the tendency of TETs toward local and regional recurrence, radiotherapy has historically been a component in the treatment strategy in the postoperative setting.[1,6–9] Unfortunately, the rarity of TETs, and the lack of prospective, randomized trials make it difficult to draw high-level evidence-based recommendations regarding its actual efficacy in terms of reduction of the risk of recurrence and death; the interpretation of retrospective data is hampered by the absence of information regarding the drivers of the clinician's decision to administer or not postoperative radiotherapy (PORT). Ultimately, the recommendation is to discuss at multidisciplinary tumor board the indications of PORT, especially in stage II and III thymomas after complete resection, a situation where virtually no evidence is available.[1]

In France, RYTHMIC (Réseau tumeurs THYMiques et Cancer; www.rythmic.org) is a nationwide network for thymic malignancies, which was recognized in 2012 by the French National Cancer Institute, as part of its rare cancers program.[10] Since then, the management of all patients diagnosed with thymic tumor has been discussed at a national multidisciplinary tumor board (MTB), which is organized twice a month, discussion of all patients diagnosed with TET is mandatory at initial management and along disease progression. Decision-making is based on the RYTHMIC recommendations, which are based on the European Society for Medical Oncology Clinical Practice Guidelines.[1] A prospective database of all patients is hosted by the French Thoracic Cancer Intergroup. Systematic pathologic review is organized for all cases discussed at the MTB, for assessment of histopathologic diagnosis, staging, and completeness of resection. PORT is thus the most frequently raised question at RYTHMIC MTBs (30% of questions asked),[6] stressing the need for higher evidence regarding the risks and benefits.

Patients and Methods

Study Design

RADIORYTHMIC is a multicenter, randomized phase III, open, 2-arm clinical trial. Patients will be randomized 1:1 to PORT or surveillance (Figure 1.) Stratification criteria include histologic grading (thymoma type A, AB, B1 vs B2, B3), stage, and delivery of preoperative chemotherapy. Patients recruitment will be mainly made through the French RYTHMIC network of 15 expert centers participating to a nationwide multidisciplinary tumor board. Follow-up will last 7 years.

Patients

Three hundred fourteen patients with completely resected, stage IIb/III thymoma according to Masaoka-Koga system, that is, pT1a with capsule invasion, until stage pT3 N0 M0 in the eighth TNM staging system, will be enrolled. The main inclusion criteria are age 18 to 75 years, World Health Organization performance status 0 to 1, histology of thymoma, complete resection, and Masaoka-Koga

stage IIb and III—this corresponds with stage pT1a with capsule invasion, until stage pT3 N0 M0 in the eighth TNM staging system TNM—after central pathologic review of the surgical specimen by the RYTHMIC expert pathology group, which is standard through the network in France. Preoperative chemotherapy is allowed with a maximum of 4 cycles; Surgery should be realized at 2 months or less after the last chemotherapy injection. The main exclusion criteria include histology of thymic carcinoma, delivery of postoperative chemotherapy, concurrent chemotherapy to radiotherapy, presence of microscopic or macroscopic residual tumor after surgery or metastases (R1 or R2 resection), uncontrolled or clinically significant pleural or pericardial effusion, and prior radiation therapy to the thorax.

Postoperative Radiotherapy

All patients in the PORT-arm should be treated either with intensity-modulated radiation therapy with high-energy photons (6–10 MV) or, in selected cases, with proton therapy. As per recommendations, the planned dose to the planning target volume will be 50.4 to 54 Gy in 27 to 30 fractions of 1.8 Gy or 25 to 27 fractions of 2 Gy. The radiotherapy will be given in once daily fractions, 5 days per week. The consensus guidelines for PORT according to the *International Thymic Malignancy Interest Group* will be followed.[11] Before a center will be activated for the trial, a dummy run will be organized. Two clinical cases (one with preoperative chemotherapy and one without preoperative chemotherapy) will be proposed to the participants. The participants will have to contour the CTV, the planning target volume and the organs-at-risk (both mandatory and nonmandatory).

A radiation planning review panel will be implemented retrospectively, with a panel of radiation oncologists, surgeons, and oncologists to assess the modalities of PORT in this study, as part of secondary objectives. The quality of surgical resection will be assessed as well.[12]

Endpoints

The primary endpoint is recurrence-free survival. The secondary objectives include (1) the assessment of local–regional recurrences, the location of local–regional recurrence in comparison with the thymectomy location and with the delivered volumes of PORT; (2) an assessment of distant sites of recurrence and time to distant recurrences; (3) an assessment of overall survival; (4) and assessment of acute and late toxicities, specifically concerning autoimmune disorders, cardiac-related events, and pulmonary function alteration according to dosimetric parameters of PORT; (5) a description of the treatment of local–regional and distant recurrences; (6) of the incidence of second cancers; and (7) the evolution of autoimmune disorders.

Ancillary analyses will include the assessment of biologic markers from the tumor and from the patient to look for prognostic factors, predictive markers of toxicity of radiotherapy, and genetic predisposition to TET; radiomics studies will be performed to identify predictive signatures correlated with clinical features and outcomes.

Follow-up

Follow-up will be conducted according to RYTHMIC guidelines, using computed tomography scans of the chest at 3 and 6 months after randomization, and every 6 months thereafter for the first 3 years after randomization, and every year subsequently. The first patient will be enrolled in January 2021, with results expected in 2028.

Statistical Analysis

A total of 314 patients are to be included (157 per arm), according to Freedman method, to observe 86 events overall, to demonstrate a 15% improvement in recurrence-free survival in case of PORT (5-year recurrence-free survival improved from 65% to 80%), with a 5% type I error risk, a 15% lack of power, and a 2-sided alternative hypothesis. One interim analysis is intended to be performed to answer the main question, when one-half the events will have occurred.

Discussion

This study will be conducted part of the French National Cancer Institute-recognized network RYTHMIC, a well-recognized organization for the management and research on thymic tumors. Patients to be included in RADIORYTHMIC will be identified through the systematic discussion of treatment at the RYTHMIC central MTB. The RYTHMIC recommendations will be updated to include enrollment of eligible patients in the trial. Besides coordinating the management of patients, treating patients, and discussions at the RYTHMIC MTB, we selected a core group of investigating sites that have a significant track record in working together on academic studies in the field of thoracic oncology, and more specifically thymic malignancies. We deciphered the local and regional patient pathways to open RADIORYTHMIC in satellite sites, especially radiotherapy facilities. Additional sites may be opened.

Conclusion

To our knowledge, RADIORYTHMIC is the first, large-scale randomized trial to the assess the role of PORT after completely resected thymoma; we implemented high quality standards for surgery, pathologic diagnosis and review, and radiotherapy to ensure results to be reliable and applicable in the clinic. Ultimately, the recent results of the LungART trial reported at the European Society for Medical Oncology 2020 meeting,[13] reporting on the absence of survival benefit, as well as some potential toxicities of PORT after resection of non–small cell lung carcinoma in a population of patients, stress the urgent need for a formal assessment of PORT in thymic malignancies.

Acknowledgments

The authors thank Pr Delphine Antoni (Strasbourg), Pr Jean-Marc Baste (Rouen), Dr Suzanna Bota (Rouen), Pr Laurent Brouchet (Toulouse), Dr Fabien Calcagno (Lyon), Dr Kim Cao (Paris), Pr Marie-Pierre Chenard (Strasbourg), Dr Eric Dansin (Lille), Dr Anne De Muret (Tours), Dr Romain Dubois (Lille), Dr Jean-Christophe Faivre (Nancy), Dr Madalina Grigoriou (Paris), Dr Maxime Heyndrickx (Caen), Dr Nicolas Jaksic (Rennes), Dr Marine Lefevre (Paris), Dr Antoine Legras (Tours), Pr Hervé Lena

(Rennes), Dr Cécile Le Naoures (Rennes), Dr Delphine Lerouge, Dr Agnès Leroux (Nancy), Dr Etienne Martin (Besançon), Dr Julie Melleroux (Toulouse), Pr Julien Mazieres (Toulouse), Dr Nicolas Milhade (Tours), Dr Laetitia Padovani (Marseille), Dr Christian Perigaud (Nantes), Pr Stéphane Renaud (Nancy), Dr Bertrand Richard de la Tour (Rennes), Dr Philippe Royer (Nancy), Dr Christine Sagan (Nantes), Dr Damien Sizaret (Tours), Dr Ecaterina Surmei (Lille), Dr Sébastien Thureau (Rouen), Dr Audrey Zaccariotto (Marseille), Pr Gérard Zalcman (Paris); and the Institut Curie support team: Claire Bertrand (promotion), Jennifer Dieppedale (datas), Véronique Gillon (clinical research department), Aline Gobillon (datas), Anne Jochem (promotion), Véronique Mosseri (clinical research department), Francis Gilles Nyasse (promotion), Marie-Laure Tanguy (statistics).

References

1. Girard N, Ruffini E, Marx A, Faivre-Finn C, Peters S. Thymic epithelial tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26(Suppl 5)):v40–55.
2. Merveilleux du Vignaux C, Dansin E, Mhanna L, et al. Systemic therapy in advanced thymic epithelial tumors: insights from the RYTHMIC prospective cohort. *J Thorac Oncol*. 2018;13:1762–1770.
3. Detterbeck FC, Stratton K, Giroux D, et al. Staging and Prognostic Factors Committee; Members of the Advisory Boards; Participating Institutions of the Thymic Domain. The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposal for an evidence-based stage classification system for the forthcoming (8th) edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2014;9(Suppl 2):S65–S72.
4. Detterbeck F. Towards a TNM-based prognostic classification for thymic tumours. *J Thorac Oncol*. 2013;8:S68.
5. Thymic tumors. *TNM Classification of Malignant Tumours*. 8th edition. Oxford: Wiley and Sons; 2017.
6. Basse C, Thureau S, Bota S, et al. Multidisciplinary tumor board decision making for postoperative radiotherapy in thymic epithelial tumors: insights from the RYTHMIC prospective cohort. *J Thorac Oncol*. 2017;12:1715–1722.
7. Forquer JA, Rong N, Fakiris AJ, Loehrer Sr PJ, Johnstone PAS. Postoperative radiotherapy after surgical resection of thymoma: differing roles in localized and regional disease. *Int J Radiat Oncol Biol Phys*. 2010;76:440–445.
8. Korst RJ, Kansler AL, Christos PJ, Mandal S. Adjuvant radiotherapy for thymic epithelial tumors: a systematic review and meta-analysis. *Ann Thorac Surg*. 2009;87:1641–1647.
9. Rimner A, Yao X, Huang J, et al. Postoperative radiation therapy is associated with longer overall survival in completely resected stage II and III thymoma: an analysis of the International Thymic Malignancies Interest Group Retrospective Database. *J Thorac Oncol*. 2016;11:1785–1.92.
10. Imbimbo M, Maury JM, Garassino M, Girard N. RARECAREnet Working Group. Mesothelioma and thymic tumors: treatment challenges in (outside) a network setting. *Eur J Surg Oncol*. 2019;45:75–.80.
11. Gomez D, Komaki R, Yu J, Ikushima H, Bezjak A. Radiation therapy definitions and reporting guidelines for thymic malignancies. *J Thorac Oncol*. 2011;6(7 Suppl 3):S1743–S17.8.
12. Detterbeck FC, Moran C, Huang J, et al. Which way is up? Policies and procedures for surgeons and pathologists regarding resection specimens of thymic malignancy. *J Thorac Oncol*. 2011;6(7 Suppl 3):S1730–S1738.
13. Le Péchoux C, Pourel N, Barlesi F, et al. LBA3_PR An international randomized trial, comparing post-operative conformal radiotherapy (PORT) to no PORT, in patients with completely resected non-small cell lung cancer (NSCLC) and mediastinal N2 involvement: Primary end-point analysis of LungART (IFCT-0503, UK NCRI, SAKK) NCT00410683. *Ann Oncol*. 2020;31:S1178..