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**RADIORYTHMIC: Phase III, Opened, Randomized Study of Post-Operative
Radiotherapy (PORT) Versus Surveillance in Stage IIb/III of Masaoka Koga Thymoma
After Complete Surgical Resection.**

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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 post-operative radiotherapy (PORT) after complete resection of localized thymoma is associated with survival benefit in patients. RADIORYTHMIC is a phase III, randomized trial aiming at comparing PORT versus surveillance after complete resection of Masaoka-Koga stage IIb/III thymoma. Systematic central pathological review will be performed prior to patient enrollment as per RYTHMIC network pathway.

Patients and Methods : 314 patients will be included; randomization 1:1 will attribute either PORT (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. Patients recruitment will be mainly made through the French RYTHMIC network of 15 expert centers participating to a nationwide multi-disciplinary tumor board. Follow-up will last 7 years. Primary endpoint is Recurrence-Free Survival. Secondary objectives include overall survival, the assessment of acute and late toxicities, and analysis of prognostic and predictive biomarkers.

Results : First patient will be enrolled in January 2021, with results expected in 2028.

Keywords : Thymoma, Post-operative 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, that distinguishes thymomas from thymic carcinomas [1]. Thymomas are more frequent than carcinomas, and are further divided into five 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 TETs are historically staged according to the Masaoka-Koga staging system [1], which has been replaced by the 8th TNM staging classification [1-5].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, while 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 towards local and regional recurrence, radiotherapy has historically been a component in the treatment strategy in the post-operative 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; interpretation of retrospective data is hampered by the absence of information regarding the drivers of the clinician's decision to administer or not Post-Operative RadioTherapy (PORT). Ultimately, 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 cancer program [10]. Since then, the management of all patients diagnosed with thymic tumor has been discussed at a national Multidisciplinary Tumour 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 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 pathological review is organized for all cases discussed at the MTB, for assessment of histopathological 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, two-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 multi-disciplinary tumor board. Follow-up will last 7 years.

Patients

314 patients with completely resected, stage IIb/III thymoma according to Masaoka-Koga system, i.e. pT1a with capsule invasion, until stage pT3 N0 M0 in the 8th TNM staging system, will be enrolled. Main inclusion criteria are age 18-75 years, World Health Organization performance status 0 to 1, histology of thymoma, complete resection, and Masaoka-Koga stage IIb and III - this corresponds to stage pT1a with capsule invasion, until stage pT3 N0 M0 in the 8th TNM staging system TNM - after central pathological 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 ≤ 2 months after the last chemotherapy injection. Main exclusion criteria include histology of thymic carcinoma, delivery of post-operative 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.

Post-Operative RadioTherapy

All patients in the PORT-arm should be treated either with Intensity-Modulated Radiation Therapy (IMRT) with high-energy photons (6-10 MV) or, in selected cases, with Proton Therapy (PT). As per recommendations, the planned dose to the planning target volume (PTV) will be 50.4-54 Gy in 27-30 fractions of 1,8 Gy or 25-27 fractions of 2 Gy. The radiotherapy will be given in once-daily fractions, 5 days per week. 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 PTV and the organs-at-risk (both mandatory and non-mandatory).

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. Quality of surgical resection will be assessed as well [12].

Endpoints

Primary endpoint is Recurrence-Free Survival. 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/ the assessment of distant sites of recurrence and time to distant recurrences; 3/ the assessment of Overall Survival (OS), 4/ the assessment of acute and late toxicities, specifically concerning auto-immune disorders, cardiac-related events, pulmonary function alteration according to dosimetric parameters of PORT; 5/ the description of the treatment of local-regional and distant recurrences, 6/ of the incidence of second cancers, 7/ the evolution of autoimmune disorders.

Ancillary analyses will include the assessment of biologic markers from the tumor and from the patient in order 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 scan of the chest, 3 and 6 months after randomization, and thereafter every six months for the first three years after randomization and every year subsequently.

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, in order to observe 86 events overall, to demonstrate a 15% improvement in RFS in case of post-operative radiotherapy (5-year RFS improved from 65% to 80%), with a 5% type I error risk, a 15% lack of power, and a two-sided alternative hypothesis. One interim analysis is intended to be performed to answer the main question, when half the events will have occurred.

DISCUSSION

The 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 for 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, discussing at the RYTHMIC MTB, we selected a core group of investigating sites which 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 assess the role of PORT after completely resected thymoma; we implemented high quality standards for surgery, pathological 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 ESMO 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.

FIGURES

Figure 1 : Study design

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involvement: Primary end-point analysis of LungART (IFCT-0503, UK NCRI, SAKK)
NCT00410683. Ann Oncol 2020; 31:S1178

Inclusion Criteria

- Age 18-75
- ECOG performance status ≤ 1
- Mandatory Pathological review
- Thymoma
- Complete resection
- Stage IIb or III disease according to the Masaoka-Koga staging system

(n = 157)

R

1:1

(n = 157)

Post-operative RadioTherapy (PORT)

- IMRT or Proton therapy
- Dose 50-54 Gy in 1,8-2 Gy daily fractions

No Post-Operative RadioTherapy

Follow-up

- As per RYTHMIC guidelines
- CT-scans every 6 months for 3 years then annually after 3 years
- Minimal follow-up of 3 years

Key Endpoints

- **Primary:**
- Recurrence-free survival
- **Secondary:**
- local-regional and distant sites of recurrence
- Overall survival
- Acute and late toxicities
- Dosimetric parameters

Stratification

- Preoperative chemotherapy
- Masaoka-Koga stage IIb vs. III
- Histology: low grade (type A, AB, B1) vs. high grade (B2, B3)