The Rare Cancer Network: ongoing studies and future strategy

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Abstract

The Rare Cancer Network (RCN) was formed in the early 1990's to create a global network that could pool knowledge and resources in the studies of rare malignancies whose infrequency prevented both their study with prospective clinical trials. To date, the RCN has initiated 74 studies resulting in 46 peer reviewed publications. The *First International Symposium of the Rare Cancer Network* took place in Nice in March of 2014. Status updates and proposals for new studies were heard for fifteen topics. Ongoing studies continue for cardiac sarcomas, thyroid cancers, glomus tumors, and adult medulloblastomas. New proposals were presented at the symposium for primary hepatic lymphoma, solitary fibrous tumors, Rosai-Dorfman disease, tumors of the ampulla of Vater, salivary gland tumors, anorectal melanoma, midline nuclear protein in testes carcinoma, pulmonary lymphoepithelioma-like carcinoma, adenoid cystic carcinoma of the trachea, osteosarcomas of the mandible, and extra-cranial hemangiopericytoma. This manuscript presents the abstracts of those proposals and updates on ongoing studies, as well a brief summary of the vision and future of the RCN.

Introduction

The Rare Cancer Network (RCN) held the *First International Symposium of the Rare Cancer Network* in Nice, France on March 21-22, 2014 (Figure 1). The congress reports of that meeting are presented in two companion papers in this issue of *Rare Tumors*. The first paper reviewed the history of the RCN and selected works published to date. This manuscript will review ongoing investigations and the future vision of the RCN membership for rare cancer research. More information on open and proposed studies can be found on the Rare Cancer Network webpage at www.rarecancer.net. A summary of published studies through 2012 can be found in the medical literature in a recent review paper in *Rare Tumors* journal. [1]

Future of the Rare Cancer Network

The Rare Cancer was founded over twenty years ago by Professors René-Olivier Mirimanoff and Mahumut Ozsahin. Although the network as completed 54 joint scientific studies and published 44 peer reviewed manuscripts, it was not until March 21-22, 2014 in Nice, France that the group held its first official group meeting. The founder, René-Olivier Mirimanoff, MD confirmed his desire to stop the chair of the RCN and proposed to restructure the website and the follow-up activities of this informal group, who since its creation worked through internet and email diffusion. All of the members agreed to proceed to the creation of the RCN Board of Directors. After the vote, Mahmut Ozsahin, MD, PhD was elected as the new president of the RCN. Yazid Belkacemi, MD, PhD and Juliette Thariat, MD, PhD became the new secretaries of the group, and the board members were as follows: René-Olivier Mirimanoff, MD, Marco Krengli, MD, Robert Miller, MD, Luciano Scandolaro, MD, Salvador Villa, MD, and Enis Ozyar, MD. The board decided to create an official RCN association, continue to its scientific activities in rare cancer management, and to hold their next meeting in Istanbul in March 2015. With further collaboration and growing members, the Rare Cancer Network will improve upon not only the variety of data available to physicians on rare malignancies, but also potentially outcomes for patients around the world.

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Ongoing studies

In a series of oral presentations, the group discussed ongoing investigations of the RCN and potential future collaborations over two days of the meeting. The results are presented in brief form below. The RCN research strategy to date has been to perform large, multi-institutional retrospective reviews in disease types who rarity prevents the acquisition of prospective data in clinical trials.

Cardiac sarcoma (J. Thariat)

The prevalence of cardiac sarcomas in autopsic series is less than 1%. Their median survival is approximately 18 months. The treatment consists of surgery when possible. The role of chemotherapy and radiation therapy is controversial, especially with respect to limiting cardiac radiation dose that is theoretically incompatible with the requirement of a tumoricidal dose for sarcoma. A recent series of 124 cases of the French Sarcoma Group suggested a benefit of radiation therapy on progression-free survival. The SARCHEART project has two aims: confirm the role of radiation therapy in cardiac sarcomas and provide guidelines with regard to dose, target volumes and technique.

This ambispective study, using both a retrospective and prospective component, starts in April 2014. All patients with cardiac sarcomas treated between 2000 and 2014 are eligible. Alerts will be sent to investigators for prospectively included cases at 6, 12, 18 and 24 months for follow up updates. Accrual will close in March 2015.[2]

Thyroid cancers (J. Thariat and X. S. Sun)

Study 1

Anaplastic/undifferentiated thyroid carcinomas have very poor prognosis, with median survival of about 10 months. The overall management is debated in terms of surgical aggressiveness, radiation modalities and role for neoadjuvant and concomitant chemotherapy (including taxanes and/or targeted therapies). The primary aim of this RCN study was to define the optimal surgery/chemo/radiation therapy strategy. Other aims were to determine whether the presence of an associated differentiated component was associated with a better prognosis. Inclusion criteria are patients receiving doses ≥40 Gy for ATC between 2000 and 2011. One-hundred forty patients have been included. At last follow-up, 18%, 19% and 29% had died with locoregional failure, metastases or both. Median locoregional control, metastasis-free survival, and survival were 16, 14 and 17 months. On multivariate analysis, surgery, chemo and higher dose to high risk clinical target volumes for locoregional control. On MVA, surgery and high dose were prognostic factors for overall survival. This study is being continued until July 2014.

Study 2

The second thyroid RCN study addresses a very controversial issue: the benefit of irradiation in select differentiated thyroid carcinomas. External beam irradiation has been less and less studied in the latest years, with failure to recruit patients in prospective trials. A recent EORTC protocol terminated early due to lack of accrual. Based on ancient data, locally advanced incompletely resected radioiodine negative thyroid cancers are thought potentially benefit from external beam radiotherapy. We designed a case control study for patients with high risk (T3-4, N+, radioiodine negative) tumor. 147 patients have been included to date. The study is being continued until September 2014.

Adult medulloblastoma (B. Atalar)

Medulloblastoma is a common malignancy in the pediatric patients with malignancies affecting the central nervous system. However, it accounts for only 1% of all adult brain tumors and the data for adults is generally reported in very small series. Thus, there is little consensus in the literature as to the optimal treatment of adult patients.[3] Due to paucity of data because of the relative infrequency of adult medulloblastoma, treatments are typically performed according to pediatric protocols. We aimed to report the outcomes, prognostic factors and the best treatment strategy of a large group of adult patients by the participation of our colleagues from RCN. This project began in late 2011 and until now we have collected the data of more than 100 patients from 8 centers. We believe we can successfully accrue further patients with the participation of other centers.

Glomus tumors (Y. Lassen-Ramshad)

Paraganglioma of the head and neck region are rare, mostly benign, neuroendocrine tumors.[4] For this retrospective study, patient-, tumor-, radiotherapy- and outcome data about 75 paraganglioma, treated with irradiation, were submitted for analysis from 12 institutions of the Rare Cancer Network. Survival, local control and late toxicity data are being analyzed. Preliminary analysis indicates that the overall survival is good and that the treatment is in general well tolerated, sometimes late recurrences can occur.

Proposed studies

Primary hepatic lymphoma (G. Ugurluer)

Primary hepatic lymphoma (PHL) is a rare and difficult to diagnose lymphoproliferative disorder. It constitutes less than 1% of all extranodal non-Hodgkin's lymphomas (NHL), and only 0.01-0.02% of all cases of NHL. Most of the cases present as a solitary lesion (50-60%). There is little consistency in the literature regarding treatment, and treatment options include surgery, chemotherapy, radiation therapy or varying combinations of these modalities.[5] The aim of study is to collect a significant number of patients to provide some information concerning the clinical outcome and the best treatment strategy.

Solitary fibrous tumors (J. Rooney)

Solitary fibrous tumors in the brain are rare

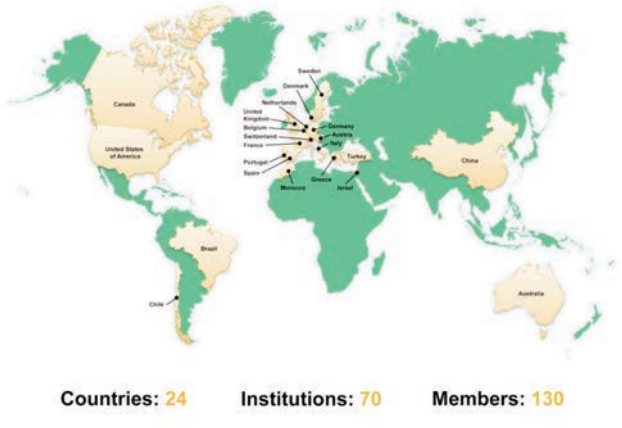

Figure 1. Geographic distribution of the Rare Cancer Network in 2014.

Figure 2. The *First International Symposium of the Rare Cancer Network*, Nice, France, March 21-22, 2014.

tumors with only 213 reported cases since it was first described in the literature in 1996.[6] Of these 213 cases, 166 involve the brain and only 8 have been reported as malignant using the criteria of high cellularity and more than 4 mitotic figures per 10 high power fields. Of these 8 cases, only 3 cases have clinical descriptions and outcomes. Due to this, a proposal was made to gather other cases with the goal of publishing a case series which would describe clinical presentations, treatment, and outcomes in order to help guide others when counseling patient regarding the possible benefits and risks of adjuvant treatment.

Rosai-Dorfman disease (K. Chang)

Sinus histiocytosis with massive lymphadenopathy, also known as Rosai-Dorfman Disease (RDD), is a rare, idiopathic disease marked by histiocyte proliferation primarily affecting the lymph nodes, though extranodal involvement is common. Diagnosis is histologically confirmed by the appearance of intact lymphocytes within large histiocytes, known as emperipolesis. While benign, localization in vital organs is potentially fatal.[7] To date, no large studies have examined the outcomes in RDD patients treated with radiotherapy. We aim to retrospectively analyze the Rare Cancer Network's experience with patients in whom RDD was managed with radiotherapy.

Tumors of the ampulla of Vater (S. Krishnan)

Ampullary cancers are rare tumors arising from the ampulla of Vater that have a distinctly better treatment outcome than pancreatic adenocarcinomas and distal cholangiocarcinomas. Whereas multiple large individual institutional series have identified clinicopathologic prognostic features of treatment outcome, they have often lacked statistical power to draw firm conclusions about the influence of tumor size, nodal status, margin status, histologic grade, and treatment choice on overall outcomes. Combining large institutional series has helped with improving statistical power and validating some of the earlier findings of prognostic markers in single-institution series.[8,9] However, none of these studies has incorporated newer information about the molecular profile of these tumors. Newer investigations based on gene expression analyses have identified two distinct subsets of patients – those with a pancreaticobiliary-like profile and consequently a poorer prognosis and those with an intestinal-like profile and a better prognosis. Analysis of the influence of such a stratification strategy on treatment outcomes for ampullary cancer would be a relatively straightforward exercise for a seasoned group of investigators at the RCN and would move the group towards more molecular/pathology-based investigations than largely clinical investigations. We therefore propose such a study as one of the larger undertakings of the group.

Salivary gland tumors (X.S. Sun and J. Thariat)

Malignant salivary gland tumors represent less than 10% of all malignant tumors of the head and neck. Tumor stage, poorly-differentiated tumors, high grade transformation, extracapsular spread, perineural involvement, vascular emboli, incomplete resection margins are unfavorable prognostic factors. The mainstay of treatment is surgery. According to the NCCN, postoperative radiotherapy can be advocated for undifferentiated and high-grade tumors, advanced disease, cases with close or positive margins, and/or in the presence of perineural invasion, lymphatic/vascular invasion, facial nerve involvement and/or deep lobe involvement. With such poor prognostic factors, high dose radiation therapy is necessary (≥65 Gy). Yet, local failure rates still approach 20% and distant metastases occur in about 20% with variable rates depending on histology and grade. The choice of concurrent chemoradiation has historically been extrapolated from data in squamous cell carcinomas. Concurrent chemotherapy (platinum given concurrently as a radiosensitizer) may improve locoregional control with high dose radiation therapy. The aim of this study is to define the benefit of adding chemotherapy to radiation therapy in salivary gland cancers depending on factors like histological subtypes.[10]

Anorectal melanoma (C. Hallemeier and D. Azria)

Mucosal melanoma of the anus or rectum is a rare tumor with aggressive behavior. For localized disease, the primary treatment is surgical excision, although outcomes following surgery remain poor. We propose a multi-institution study examining outcomes, prognostic factors, and the role of adjuvant therapies for this rare malignancy.

Midline nuclear protein in testes carcinoma (R. Funk)

Nuclear protein in testes (NUT) Midline Carcinoma (NMC) presents as a rapidly progressive, poorly differentiated carcinoma of the head and neck or midline thorax structures with a predilection for younger patients and with a median survival of 6.7 months. Since NUT (nuclear protein in testes) expression in normal tissue is limited to testes, detection of NUT in carcinoma cells (with a commercially available monoclonal antibody) is diagnostic.[11] Because the biologic underpinnings defining NMC were only recently discovered, little is known about effective treatment strategies for this rare and aggressive disease. We encourage Rare Cancer Network participants to consider this diagnosis in patients with poorly differentiated carcinomas of epithelial origin and to collect details regarding presentation, diagnosis, therapy and outcomes for inclusion in an RCN study.

Pulmonary lymphoepithelioma-like carcinoma (L.J. Zhang)

Pulmonary lymphoepithemlioma (LELC) is a distinct group of non-small cell lung cancer (NSCLC) that appears to affect younger, nonsmoking patients, and should be pathologically confirmed by Immunohistochemistry and hematoxylin-eosin staining. The diagnosis of pulmonary LELC should exclude the primary occurrence of nasopharyngeal carcinoma (NPC) due to the similarity of morphology and EB virus-susceptibility.[12] Genetic variations observed in patients with NSCLC are rare in LELC patients. Pulmonary LELC patients may receive a survival benefit from multimodality treatment.

Adenoid cystic carcinoma of the trachea (P. van Houtte)

Primary tracheal cancers are uncommon disease representing 0.4% of all cancers and primary adenoid cystic carcinoma represents less than 10%.[13] Most series covered a long period and included mainly surgical cases with or without radiotherapy. Series of patients treated by radiation alone are often case reports including a few patients. The aim of this study is to have more data on the role of radiation therapy especially through looking to patients treated during the last two decades with modern technology and staging procedure.

Osteosarcomas of the mandible (J. Thariat)

The literature suggests that head and neck osteosarcomas behave differently from limb osteosarcomas and that there is a role for radiation therapy in incompletely resected facial osteosarcomas. The RCN study on mandibular osteosarcomas aimed to determine whether head and neck osteosarcomas behaved similarly as limb osteosarcomas and whether intermediate grade behaved like high grade osteosarcomas. The population was restricted to the mandibular location because this location usually allows wide resection margins (with reconstructive surgery). It might thus more easily help state on surgical practice and the role of radiation therapy in patients with completely resected tumors (including those with no residual disease after neoadjuvant chemotherapy). The study (n=111) suggested to performed similar treatment in intermediate and high grades. It confirmed the role of surgery and showed a benefit of chemotherapy on survival rates, but failed to provide an

answer for the role of radiotherapy (only one 5th of patients underwent radiation therapy). The study is thus being continued to more specifically address the role of radiation therapy. Additionally, Prof Brouchet-Gomes, bone sarcoma pathologist in Toulouse, has accepted to check the pathologic reports, and to review blocks and perform molecular analyses.[14]

Extra-cranial hemangiopericytoma (M. Krengli)

Hemangiopericytoma is a rare disease presenting in most of the cases with intracranial location. Data on extracranial hemangiopericytoma come mainly from general reviews and case reports.[15] The purpose of the proposed RCN study is to investigate clinical presentation, pathology features, treatment modalities, and outcome in terms of local control and survival of extracranial hemangiopericytoma. Special attention will be paid to the role of radiotherapy in the treatment of this rare tumor.

Other studies

In addition to the studies listed above, the RCN is currently has ongoing studies in the subjects of male ductal carcinoma *in situ* of the breast and lacrimal gland adenoid cystic carcinoma. Further information can be found on the RCN website at www.rarecancer.net.

Issues in future research and conclusions

The RCN has been dedicated in defining the role of radiation therapy in rare tumors with investigators from all over the world. Institutional review board approval across countries is critical and RCN radiation oncologists have been very strict in obtaining IRB for their studies. Regulations are changing and investigators are requested to ask for patient consent if required to comply with their own country regulations (that can be waived for deceased patients in some nationalities). RCN studies have been retrospective but there are some suggestions that ambispective studies, utilizing both retrospective and prospective data acquisition, can be of help for diseases with median survival of 2 years or less; provided that alerts can be sent to investigators for follow up updates. Also, case control studies including case patients that are irradiated and control patients that are not may be useful to limit selection biases and provide even higher level of evidence for the role of radiation therapy in rare diseases, adding to the major contributions of the RCN to radiation therapy. The role of irradiation will also be regarded with respect to technological advances.

The rapidly decreasing costs of genomic characterization promises a new opportunity for rare tumor research that may allow for characterization of potential chemotherapeutic targets for novel agents utilizing relatively small sample sizes. Genomic profiling raises the possibility of every tumor type becoming *rare* through its unique genetic makeup.[16] Additionally, advances in electronic medical records and analytics may permit large population based studies with more discrete endpoints than have been possible in the past with resources such as the SEER database. The RCN will need to evolve in structure and function to incorporate these new analytical tools in order to retain its relevance in the 21st century in area of increasing personalization of medical science.

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