

## The Rare Cancer Network: achievements from 1993 to 2012.

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### Abstract

The Rare Cancer Network (RCN), founded in 1993, performs research involving rare tumors that are not common enough to be the focus of prospective study. Over 55 studies have either been completed or are in progress.

The aim of the paper is to present an overview of the 30 studies done through the RCN to date, organized by disease site. Five studies focus on breast pathology, including sarcoma, lymphoma, phyllodes tumor, adenoid cystic carcinoma, and ductal carcinoma *in situ* in young women. Three studies on prostate cancer address prostatic small cell carcinoma and adenocarcinoma of young and elderly patients. Six studies on head and neck cancers include orbital and intraocular lymphoma, mucosal melanoma, pediatric nasopharyngeal carcinoma, olfactory neuroblastoma, and mucosa-associated lymphoid tissue lymphoma of the salivary glands. There were 4 central nervous system studies on patients with cerebellar glioblastoma multiforme, atypical and malignant meningioma, spinal epidural lymphoma and myxopapillary ependymoma. Outside of these disease sites, there is a wide variety of other studies on tumors ranging from uterine leiomyosarcoma to giant cell tumors of the bone. The studies done by the RCN represent a wide range of rare pathologies that were previously only studied in small series or case reports. With further growth of the RCN and collaboration between members our ability to analyze rare tumors will increase and result in better understanding of their behavior and ultimately help direct research that may improve patient outcomes.

### Introduction

The Rare Cancer Network (RCN), which was founded in 1993 by Professor René Mirimanoff in Lausanne, started as an infor-

mal, well-organized group of radiation oncologists, from all over the world. The RCN was made possible by the revolution in electronic communication that occurred in the 1990's. Rapid communication through e-mail and a dedicated web site ([www.rarecancer.net](http://www.rarecancer.net)) permitted researchers across the globe to come together in an informal network dedicated to the study of rare cancers.

The RCN has typically studied malignancies that are too rare to be the focus of prospective clinical trials. Although the results generated by RCN's pooled studies reflect their retrospective and multi-institutional nature, with all the biases that these limitations imply, they may represent the highest level of evidence available in the hierarchy of the evidence base, nonetheless.

Herein, we report a summary of the past studies of the RCN that have undergone peer review and publication.

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**Figure 1. Location of Rare Cancer Network Primary Investigators in Europe, Asia (A) and North America (B) for studies published 1993 to 2011.**

## Materials and Methods

The Rare Cancer Network consists of 130 investigators in 24 countries (Supplementary Table 1).

Membership is available for any clinical investigator interesting in collaboration with the network. Members can propose research topics of rare cancers to the RCN coordinating office to survey the rest of the membership for level of interest.

All studies undergo required review by ethics or institutional review boards at each participating institution. Data is then extracted from existing cases locally at each department according to flow sheets designed by the primary investigator. This data is then pooled through electronic means for analysis. Authorship is a function of case contribution, with author rank determined by the relative number of patients contributed to each individual study.

The studies reported in this article were identified from the RCN web site ([www.rarecancer.net](http://www.rarecancer.net)) and through online searches of PubMed.

## Results

Currently there are 55 studies either completed or in progress, including data from over 3500 patients, resulting in 28 peer reviewed publications. The median study size was 81 (ranging from 9 to 443). All studies were multi-center retrospective reviews. The studies focused on rare cancers or rare presentations of common cancers. The malignancies covered were of a wide variety with fair distribution among anatomic location and histology. Figure 1 illustrates the geographic location of study primary investigators.

## Studies

### Breast

Five studies have focused on rare breast pathologies as are outlined in Table 1.<sup>1-5</sup>

The cancer studies include breast sarcomas, lymphoma, phyllodes tumor, ductal carcinoma *in situ* (DCIS) in young women, and adenoid cystic carcinoma. These were all multicenter, retrospective analyses with a median study size of 103 (range 61-443). Radiotherapy of some form was found to be associated with an improved outcomes in all breast studies except for the Bousquet *et al.* sarcoma study, a study which focused primarily on prognostic factors.<sup>1-5</sup>

### Prostate

There have been three multi-center retrospective studies that have focused on prostate cancers as outlined in Table 2.<sup>6-8</sup>

Two studies done by Nguyen *et al.* have specifically addressed treatment of prostate adenocarcinoma in the rare populations of young (<55 years) and older (>80 years) patients.<sup>6,7</sup> For younger patients, the researchers found that patients treated with external beam radiotherapy had similar local control rates as those undergoing radical prostatectomy.<sup>6</sup> For older patients, they found no negative impact of curative radiotherapy on disease free survival and overall survival, concluding that radiotherapy in this group of elderly patients with localized tumors was not associated with increased toxicity or poor tumor control rates.<sup>7</sup>

A third article by Stein *et al.* studied the treatment of small cell carcinoma of the prostate, concluding that the overall prognosis of the disease was poor and combined modality therapy with cisplatin and radiotherapy was not associated with improved outcomes, even after a promising initial response in some patients.<sup>8</sup>

### Head and neck

Six studies reviewed multi-center data for several different head and neck cancers as detailed in Table 3.<sup>9-14</sup>

**Table 1. Rare Cancer Network studies of breast cancers.**

Breast	Author	Year	Cases	Results
Boost radiotherapy in young women with DCIS	Omlin <sup>1</sup>	2006	373	Local relapse free survival at 10 years: 46% w/ no RT, 72% w/ RT no boost, 86% w/ RT+boost
Outcome and prognostic factors in breast sarcoma	Bousquet <sup>2</sup>	2007	103	5 year survival: disease free-44, over all- 55%. favorable prognostic factors in multivariate for LC: no residual tumor, no cellular pleomorphism, and non angiosarcoma histo. For DFS, non menopausal status, no residual tumor after tx, non-angio histo, absence of tumor necrosis and lower grade
Phyllodes tumor of the breast	Belkacemi <sup>3</sup>	2008	443	Benign tumors have good prognosis after surgery alone. For malignant and borderline group, RT decreased LR and total mastectomy had better results than conservational surgery
Management of adenoid cystic carcinoma of the breast	Khanfir <sup>4</sup>	2011	61	For conservation group, RT improved 5-year LRC to 95% from 83%
Primary breast lymphoma: patient profile, outcome, prognostic factors	Jeanneret-Sozzi <sup>5</sup>	2008	84	5yr survival: overall-53%, lymphoma specific- 59%, disease-free 41%, local control- 87%. Univariate analysis: favorable prognostic factors- early stage, conservative surgery, RT, combined modality

**Table 2. Rare Cancer Network studies of prostate cancer.**

Prostate	Author	Year	Cases	Results
Curative role of radiotherapy in adenocarcinoma of the prostate in patients under 55	Nguyen <sup>6</sup>	2005	39	Similar local control in younger and older patients from either EBRT or radical prostatectomy
Prostate cancer in patients aged 80 or more	Nguyen <sup>7</sup>	2009	65	No negative impact of radiation on disease free survival and global survival
Small cell carcinoma of the prostate: etiology, diagnosis, prognosis, and therapeutic implications	Stein <sup>8</sup>	2008	30	Cisplatin+RT failed to improve outcome after good initial response

This diverse group includes a pediatric study analyzing nasopharyngeal carcinoma, a rare disease for which an optimal treatment has not been found.<sup>12</sup> The study, the largest of its kind, finds that patients had received combined therapy with chemotherapy and radiation had the longest survival.

The study also found evidence suggesting that a lower radiotherapy dose could be considered in patients with a good response to chemotherapy, although no definitive conclusions could be made given the retrospective nature of the study. Anacak *et al.* reported the largest series to date of patients with mucosa-associated lymphoid tissue (MALT) lymphoma of the salivary glands.<sup>10</sup> The researchers found that patients treated with radiotherapy were observed to have increased disease-free survival.

Treatment with both radiotherapy and surgery was associated with an improved outcome, both in a review of patients with olfactory neuroblastoma by Ozsahin.<sup>13</sup> A similar relationship was found for mucosal melanoma patients by Krengli and Mirimanoff.<sup>11</sup>

### Central nervous system

The RCN has completed four series on rare cancers of the central nervous system (Supplementary Table 2).

A study by Weber on cerebellar glioblastoma multiforme included 45 patients and found that all patients had local progression.<sup>15</sup> Pasquier *et al.* reviewed 119 patients with atypical and malignant meningiomas whom all received radiotherapy and found 5 and 10-year survival rates to be 65% and 51%, respectively.<sup>16</sup>

On univariate analysis, the authors found survival was negatively affected by age >60, poor performance status, and a high mitotic rate. Fifty-two patients with spinal epidural lymphomas were evaluated in a study by Mirimanoff and were found to have good response to chemoradiation *versus* radiation alone.<sup>17</sup>

In patients with spinal myxopapillary ependymoma, post-operative radiotherapy had a significant increase in 5-year progression free survival (82%) when compared to surgery alone (50%).<sup>18</sup>

### Other

There are various other studies done by the RCN as listed in Table 4.<sup>19-30</sup>

These studies vary from thyroid lymphomas to uterine papillary sarcomas (Supplementary Table 3).

## Discussion

Rare cancers present a challenge to the scientific investigator.<sup>31</sup> Their rarity typically pre-

vents the conduct of adequately powered clinical trials or definitive study by any single individual or institution. Multi-institutional efforts can increase the volume of clinical data available for rare cancer studies, but such efforts must compete with more common malignant entities for funding.

Although studying rare cancers through prospective clinical trials is possible, as evidenced by the work of the Children's Oncology Group, most adult rare cancers have not been the focus of a therapeutic clinical trial.

Population based registries such as the Surveillance Epidemiology and End Results database ([www.seer.cancer.gov](http://www.seer.cancer.gov)) can provide descriptive data on prevalence and outcomes, but they are not designed to address specific treatment related hypotheses in the manner of clinical trials. Continued evolution of health care informatics and population based care delivery may provide increasing levels of outcomes data on rare malignancies.

Recently, the International Rare Cancer Initiative was formed through a collaboration of EORTC, Cancer Research UK, the National Institute for Health Research Cancer Research Network (NCRN), and the United States National Cancer Institute (NCI). This organization will focus on designing clinical trials of

treatments for rare cancers and should improve upon the quality of evidence in the future. By pooling resources and patient cohorts internationally through the infrastructure of existing national cancer research programs, it will provide valuable prospective data on a limited number of rare tumor entities such as small bowel cancer, rare head and neck cancers, gynecological sarcoma, fibromellar hepatocellular carcinomas, and penile carcinoma. (<https://wiki.nci.nih.gov/display/ICWG/US-UK-EORTC+Rare+Cancer+Initiative>).

Additionally, patient advocacy organization such as the National Organization for Rare Disorders ([www.rarediseases.org](http://www.rarediseases.org)) and Rare Disease Europe ([www.eurordis.org](http://www.eurordis.org)) aid in the fight against rare malignancies.

The Rare Cancer Network was founded in 1993 to provide a multi-institutional framework to facilitate rare cancer research, with a focus on the specific role of radiation therapy, through pooled data analysis by participating academic medical centers across the world.

In the last 19 years, the RCN has studied many different rare cancers that previously only had small series or case reports. With pooling of data from around the world, the network was able to produce a number of studies for which meaningful clinical data is lacking

**Table 3. Rare Cancer Network studies of head and neck cancers.**

Head and neck	Author	Year	Cases	Results
Outcome and prognostic factors in orbital lymphoma	Martinet <sup>9</sup>	2003	90	Moderate to low-dose RT (<34 Gy) alone controls primary orbital lymphoma with low morbidity
Abstract: Outcomes and prognostic factors in primary intraocular lymphoma	Mak <sup>10</sup>	2007	20	5-year overall, disease free survival, and local control rates of 55,39,72%. high rate of CNS recurrence (51% at 5-years). Vitreous involvement=worse prognosis. CNS prophylaxis and more aggressive therapies need to be considered
Radiotherapy in the treatment of mucosal melanoma of the upper aerodigestive tract	Mirimanoff <sup>11</sup>	2006	74	Local control at 3 years- 57% with surgery and 71% after surgery and RT
Treatment results of 165 pediatric patients with non-metastatic nasopharyngeal carcinoma	Ozyar <sup>12</sup>	2006	165	5-year overall survival 77.4%, disease free-68.8%. Combined RT and chemotherapy was optimal treatment
Outcome and prognostic factors in olfactory neuroblastoma	Ozsahin <sup>13</sup>	2010	77	5 year survival: overall- 64%, disease free- 57, locoregional-62, local control- 70. Surgery and post-op RT (>53Gy) had best outcome. Concomitant chemo+/-higher dose RT should be prospectively investigated
Primary mucosa-associated lymphoid tissue lymphoma of the salivary glands	Anacak <sup>14</sup>	2010	63	5 year disease free, disease specific, and overall survival- 54.4,93.2,81.7%. Recurrences may occur in up to 35% of patients at 5 years, survival not affected. RT only modality that improved disease- free survival

**Table 4. Rare Cancer Network studies of other tumors.**

Cancer	Title	Author	Year	Cases	Results
Thyroid lymphoma	Treatment results and prognostic factors in primary thyroid lymphoma patients	Ozyar <sup>9</sup>	2011	87	5, 10 year overall survival 74, 71% and DFS 68, 64%. Combined modality treatment improves prognosis for aggressive lymphoma, but does not improve OS and LC in indolent lymphoma
ALCH bones	Adult langerhans cell histiocytosis of bone	Ozyar <sup>20</sup>	2010	30	Complete remission in 70%. Recurrence rates lower in those treated with surgery and RT
Giant cell tumors of bone	Radiotherapy for marginally resected, unresectable, and recurrent giant cell tumors of bone	Bhatia <sup>21</sup>	2007	39	5-year local failure rate 21%. 5 year OS 94%. Radiotherapy provided excellent long-term local control
Erdheim-Chester disease	Palliative treatment of Erdheim-Chester disease with RT	Miller <sup>22</sup>	2006	9	EBRT provided short-term palliation in terms of pain control with most cases experiencing recurrence
Solitary plasmacytoma	Outcomes and patterns of failure in solitary plasmacytoma	Ozsahin <sup>23</sup>	2006	258	Extramedullary SP had better outcomes with moderate dose RT. Progression to myeloma remains issue with medullary disease
Desmoid tumors	Impact of radiotherapy in treatment of desmoid tumours	Baumert <sup>24</sup>	2006	110	Post-op RT significantly improved 5-year PFS (47% vs 13% for surgery alone)
Non-small cell lung cancer	Exclusive radiotherapy for non-small cell lung cancer	Gouders <sup>25</sup>	2003	123	2 and 5 year survival- 34, 8%. 5-year local failure rate for T1,T2 - 42%/82%
Urothelial renal pelvis and ureter tumors	Prognostic factors in urothelial renal pelvis and ureter tumours	Ozsahin <sup>26</sup>	1999	138	Survival influenced by: Karnofsky performance index, pT- and pN-classification, utereral localization, histologic grade, and existence of tumor after surgery
Papillary serous carcinoma	Outcome after combined modality treatment for uterine papillary serous carcinoma	Goldberg <sup>27</sup>	2007	138	Radiotherapy reduced pelvic recurrence from 29% to 14%. Suggest conservative surgery followed by adjuvant chemo and pelvic RT
Uterine leiomyosarcoma	ABSTRACT: primary uterine leiomyosarcoma: outcomes and prognostic factors	Franzetti Pellanda <sup>28</sup>	2001	80	Adjuvant radiotherapy did not improve survival or local control. Brachytherapy increased treatment related morbidity.
Testicular lymphoma	Outcome and patterns of failure in testicular lymphoma	Zouhair <sup>29</sup>	2002	36	Combined modality treatment improved survival. RT technique or dose did not change outcome
Primary anal canal adenocarcinoma	Management of primary anal canal adenocarcinoma	Belkacemi <sup>30</sup>	2003	82	Combined RT/CHT resulted in better survival rates. Recommend APR for salvage treatmentonly

on treatment outcomes.

Although such studies cannot rank with randomized controlled trials in terms of impact, they do fill an important niche in between anecdotal evidence and clinical trials *in situ* situations where a tumor's rarity prevents prospective study.

The multicenter and retrospective nature of the studies can be seen as a significant limitation on the conclusions of the studies due to the variability of treatment, technique, and population in different departments around the world. However, as noted previously, for many rare cancers, it would be difficult if not impossible to study such tumors in a cost-efficient fashion prospectively. The data and results from the RCN studies serve to shed sufficient light to advance the care for the unfortunate patients that are diagnosed with these rare diseases.

With further collaboration and growing members, the Rare Cancer Network can improve upon not only the variety of data avail-

able to physicians on rare malignancies, but also potentially outcomes for patients around the world.

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