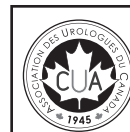


# A Canadian approach to the regionalization of testis cancer: A review



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**Summary of the Canadian Testis Cancer Workshop (November 15–17, 2018; Toronto, ON, Canada)**

## Abstract

At the Canadian Testis Cancer Workshop, the rationale and feasibility of regionalization of testis cancer care were discussed. The two-day workshop involved urologists, medical and radiation oncologists, pathologists, radiologists, physician's assistants, residents and fellows, and nurses, as well as patients and patient advocacy groups.

This review summarizes the discussion and recommendations of one of the central topics of the workshop — the centralization of testis cancer in Canada. It was acknowledged that non-guideline-concordant care in testis cancer occurs frequently, in the range of 18–30%. The National Health Service in the U.K. stipulates various testis cancer care modalities be delivered through supra-regional network. All cases are reviewed at a multidisciplinary team meeting and aspects of care can be delivered locally through the network. In Germany, no such network exists, but an insurance-supported online second opinion network was developed that currently achieves expert case review in over 30% of cases. There are clear benefits to regionalization in terms of survival, treatment morbidity, and cost. There was agreement at the workshop that a structured pathway for diagnosis and treatment of testis cancer patients is required.

Regionalization may be challenging in Canada because of geography; independent administration of healthcare by each province;

physicians fearing loss of autonomy and revenue; patient unwillingness to travel long distances from home; and the inability of the larger centers to handle the ensuing increase in volume. We feel the first step is to identify the key performance indicators and quality metrics to track the quality of care received. After identifying these metrics, implementation of a “networks of excellence” model, similar to that seen in sarcoma care in Ontario, could be effective, coupled with increased use of health technology, such as virtual clinics and telemedicine.

## Introduction

Testis cancer is the most common solid organ cancer in men aged 15–29 years, with an estimated 1100 men diagnosed annually in Canada. Between 60–80% of testis cancers present as clinical stage 1 (organ confined) disease and the five-year survival from testis cancer in Canada is 96%.<sup>1</sup>

The first Canadian Testis Cancer Consensus Conference in 2007 resulted in the Canadian consensus guideline, published in 2010, which gave direction on the diagnosis and multidisciplinary management of testis cancer.<sup>2</sup> Although the terminology ‘regionalization of care’ was not directly used, one of the emerging themes of the first conference and guideline was the importance of testis cancer care occurring at centers with volume and experience.

In November 2018, we convened the second Canadian Testis Cancer Workshop. This two-day meeting was attended by urologists, medical and radiation oncologists, pathologists, radiologists, physician's assistants, residents and fellows, nurses, patients, and patient advocacy groups — all with an interest in testis cancer. The rationale for regionalization of testis cancer care in Canada was the one of the lead topics, with the following questions addressed.

## How often does testis cancer patient care deviate from published guidelines?

The management of testis cancer patients requires a concerted multidisciplinary approach. Despite regularly updated guidelines regarding the management of testis cancer,<sup>2-4</sup> non-guideline-based care occurs. Paffenholz demonstrated that 18% of patients at a German center received non-guideline-concordant treatment, including under-treatment (due to missed chemotherapy cycles), which negatively impacted relapse-free survival rates.<sup>5</sup> Similarly, non-guideline-directed care was demonstrated in 30% of patients at three referral centers in the U.S., leading to delayed definitive therapy, unnecessary morbidity associated with overtreatment, and higher rates of relapse.<sup>6</sup>

## What is regionalization?

There is no consensus definition of regionalization. It involves the integrated organization of a healthcare system possessing multiple coordinated functions and serving a limited geographical territory. Three main features have been described: coordination, de-centralization, and rationalization of resources.<sup>7</sup>

A recent systematic review of the centralization of care for genitourinary malignancies by high-volume providers was associated with greater use of cancer surgery, lower morbidity, and better survival outcomes.<sup>8</sup> Centralization of care for testis cancer patients has yielded favorable outcomes according to SWENOTECA (Swedish and Norwegian Testicular Cancer group) and DATECA (Danish Testicular Cancer group).<sup>9,10</sup> The low population density, public healthcare system, and rarity of testis cancer in Scandinavia mean that centralization is feasible.

In the U.S., Macleod et al, in an analysis of the National Cancer Database, demonstrated that regionalization of testis cancer was associated with decreased diagnostic delays, earlier stage at diagnosis, and improved survival.<sup>11</sup>

Currently, in Canada, although there are consensus guidelines regarding the management of testis cancer, there is no defined regionalization of care. The challenge remains as to whether regionalization is possible, who would benefit from it, and how to provide this service.

## What happens currently in other jurisdictions?

The National Health Service (NHS) in the U.K. is a similar publicly funded, single-payer health service, although Canada's providers are usually private. In 2002, the National Institution for Clinical Excellence (NICE) released a manual, "Improving outcomes in urological cancers." They recommended the development of networks to provide and coordinate a wide range of services for patients with urologi-

cal cancers within a defined geographical area. Different degrees of specialization were required to deal with the various types of cancer, and multidisciplinary teams (MDTs) were recommended to be established in cancer units, cancer centers, and at the supra-network level.<sup>12</sup>

Professor Robert Huddart, clinical oncologist at the Royal Marsden Hospital in London, described the testis cancer network they provide for South-East of London with a catchment population of approximately 5 million. There are approximately 15–20 such testis cancer centers in the U.K., each managing about 100 new cases per year. These are divided into local, regional, and supra-regional centers to provide multidisciplinary care for patients at all points in their testis cancer journey. The MDT consists of at least two urologists, a clinical oncologist, a medical oncologist, a specialized radiologist and pathologist, clinical nurse specialist, and an MDT coordinator. There is a weekly MDT meeting in which all new cases and recurrent patients are discussed. The NICE guideline stipulates the initial diagnosis and management (radical orchiectomy) can be provided locally and then referral to the testis cancer network within 24 hours after surgery unless there is evidence of de novo metastatic disease.

Professor Peter Albers discussed the management of testis cancer in Germany, where there is a similar lack of regionalization as in Canada. Since 2006, however, a unique online second opinion network was developed to allow urologists to seek expert opinion from a designated second opinion provider. Professor Albers reported data from the network, demonstrating discordance between the primary and expert opinion in up to 39.5% of cases (even in clinical stage 1) with a change in treatment plan in 17.3%.<sup>13</sup> Thus, nearly one in five new testis cancer cases benefited from having their case reviewed at the second opinion network. This system has since become funded by insurance companies for the primary physician, which incentivizes an expert opinion, and it currently captures approximately 30% of new cases.

In November 2016, the European Society for Medical Oncology convened a testis cancer consensus conference. One of their key recommendations was that outside of an orchiectomy, treatment of patients with testis cancer should be conducted in high-volume centers.<sup>14</sup> They advocated the benefits of centralized care to include a pathological review of orchiectomy or other tissue material when needed; specialist radiological evaluation at diagnosis, post-chemotherapy, and during followup; guideline-based indication and delivery of chemotherapy and surgery by expert teams; all of which might be crucial for success.

## What are the benefits to regionalization of testis cancer?

The treatment of metastatic testis cancer at lower-volume centers has been associated with poor survival.<sup>15</sup> Reasons

for this survival difference are multifactorial and span issues with chemotherapy and radiotherapy delivery, surgery and perioperative care, pathology and radiology expertise, and supportive care. Both overtreatment and undertreatment are prevalent. Wymer et al reported poor adherence to NCCN guidelines at three established referral institutions in the U.S. Non-guideline-directed care was identified in 30% patients. Overtreatment (40%) was one of the most common reasons for discordant care, though undertreatment (16%) occurred frequently as well.<sup>6</sup> Adherence to guidelines may translate into improved relapse rates and survival,<sup>6</sup> but it is important to note that benefits of regionalization may manifest not only in minimizing over- or undertreatment. Given the young age of testis cancer patients and the excellent survival, it is appropriate to focus efforts and resources to ensure quality of life is optimized by minimizing over- or undertreatment.

Retroperitoneal lymph node dissection (RPLND) is a complex and nuanced surgery, with a possibility for high morbidity/mortality. Surgery performed at a high-volume center of excellence has well-established benefits. Capitano compared post-chemotherapy (pcRPLND) performed at Indiana University (a recognized high-volume testis center) to pcRPLND performed elsewhere (as captured by the Surveillance, Epidemiology and End Results [SEER] database). The perioperative mortality rate for a pcRPLND at Indiana University was 0.8% compared with 6% in the SEER database.<sup>16</sup> Similar differences were noted in France, where pcRPLND performed by a single high-volume surgeon was compared to 66 low-volume surgeons. There were differences in perioperative mortality (7% vs. 16%), negative margins (93% vs. 75%), and recurrence rates (7% vs. 16%).<sup>17</sup> Hospital volume was also associated with improved survival in Japan, suggesting it was not just about surgical experience but also experience in all team members and infrastructure involved in perioperative care.<sup>18</sup>

The nuances of chemotherapy with different regimes and dose intensity for risk strata have significant implications with respect to the morbidity and prognosis.<sup>19</sup> The long-term effects of chemotherapy increase proportionally with the number of cycles given,<sup>20,21</sup> which hypothetically may be improved with standardization of care. The SWENOTECA group demonstrated a risk-adapted approach to chemotherapy in non-seminomatous germ cell tumors (NSGCT) patients to maintain oncological outcomes while minimizing toxicity of overtreatment.<sup>22,23</sup> Regionalization of care will allow dedicated centers to recommend the most appropriate chemotherapy regimen for patients.

There are also economic benefits to guideline-concordant care. In the short-term, choosing and administering a treatment with the least complications can influence care cost dramatically. For example, re-admissions after surgery, in-patient stays to manage chemotherapy-related complications, unnecessary courses of radiation, and over-imaging on

surveillance could manifest in increased costs in the short-term.<sup>16,17,24</sup> In the longer-term, treatment-related complications can lead to a lifetime of increased medical expense. The increased risk of heart disease, second malignancies, and metabolic syndrome associated with chemotherapy and radiotherapy mean that decisions regarding which treatments and number of cycles have large cost implications 30 and 40 years later.<sup>24</sup>

## Is regionalization possible in Canada?

The consensus was 'yes,' regionalization is possible. For example, in Ontario, Canada's largest province by population, Cancer Care Ontario (CCO) has been successful in regionalizing the care of several cancers. Thoracic surgery for esophageal cancer and lung cancer is an example. An expert panel was convened by CCO in 2004 with the aims to maintain the high quality of care in current centers of excellence, to strengthen care in newly designated centers, and to encourage discontinuation of thoracic surgical procedures in centers not meeting the predefined standards.<sup>25</sup> The objective of regionalization was to achieve 90% compliance of pulmonary and esophageal cancer resections being performed in designated centers by the end of 2010.

In their report, they designated centers and outlined certain standards, such as number of surgeons and volume per center, and defined performance measures, such as perioperative mortality and wait times. A database was also developed to analyze their performance. Before regionalization (2004), 46 hospitals performed thoracic surgical procedures. By 2010, 13 tertiary and two secondary (a center with a formal referral pathway to a tertiary center) centers were designated to perform thoracic surgery, and in the final year of the analysis (2009–2010), 89% esophagectomies and 94% of lung resections were being performed in the designated centers. Regionalization achieved a significant reduction in 30-day mortality for pneumonectomy but no change for esophagectomy or lobectomy.<sup>26</sup> Regionalization of care in Ontario has also been addressed to varying degrees in the fields of sarcoma, lung cancer,<sup>27</sup> pancreatic cancer,<sup>28</sup> cardiac surgery,<sup>29</sup> and palliative care.<sup>30</sup> British Columbia has adopted similar regionalization, for example, in trauma care<sup>31</sup> and a home oxygen program.<sup>32</sup>

The management of sarcoma in Ontario has been one of the successful implementations of regionalization. Quality sarcoma care includes pathology review at the host center by pathologists with a specialty or special interest in sarcoma, molecular diagnostics, site-specific imaging, advanced limb salvage and abdominal surgery, high-precision radiotherapy, and the delivery of chemotherapy regimens. In Ontario, sarcoma services are organized through three multi-regional collaborative sarcoma programs, centered in Toronto, Hamilton, and Ottawa.<sup>33</sup> Each program has a

host site, which provides a full spectrum of specialized sarcoma services. Partner sites and hospitals in partner regions provide a subset of services appropriate to their level of expertise and under stewardship of the host site. The partner center is involved with the diagnosis but must receive a central pathology review. They can also provide radiation treatment, non-complex surgery, and adjuvant chemotherapy after discussion with the host site. The other centers in the partner region are involved with diagnostic imaging, delivery of chemotherapy, palliative radiotherapy, and rehabilitation. The purpose of this provincial sarcoma plan is to provide all patients in Ontario, no matter where they reside, access to comprehensive sarcoma services.

CCO has recently published a report on complex surgery in the retroperitoneum (RPLND).<sup>34</sup> One of their recommendations is that patients should be referred to higher-volume centers for resection.

### What is Canada's challenge in regionalization?

Canada has numerous obstacles to regionalization — some are unique to Canada, while others are shared with countries that have successfully implemented forms of regionalization. The barriers include: 1) vast geography; 2) independent and siloed administration of healthcare by each province; 3) physician/provider fear of loss of autonomy and revenue; 4) patient unwillingness or inability to travel long distances from home for assessment and treatment; 5) inability of the large centers to handle the ensuing increase in volume; and 6) the formidable capital investment that would be required to implement organization and infrastructure for regionalization (e.g., patient navigators, coordinators, e-health systems, etc.) in a system that is currently cash-strapped. Canada is the second largest country in land mass in the world yet ranks 38<sup>th</sup> in population. This translates into a population density that ranks 230<sup>th</sup>. Immediately one can see how geography is a formidable challenge to regionalization compared to Scandinavia, the U.K., or Germany, where aspects of regionalization have been well-adopted (Table 1).

The Atlantic provinces, which includes New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador, were discussed as an example. The area has a population of approximately 2.4 million people, with 60

new testis cancer cases per year. By comparison, this is half the number of new cases per year seen by the Royal Marsden Cancer Centre Network in London, described by Professor Huddart. Geographically, however, the land mass of the Atlantic provinces is equivalent to the U.K. and Germany combined. The Canadian challenge is how to provide the highest level of cancer care to 60 patients across four vast provinces with a 40–50% rural population and the lowest yearly incomes in Canada.

A regionalization policy where all testis cancer patients in Atlantic Canada are seen, treated, and followed in Halifax (the largest city in Atlantic Canada) is not feasible. A Canadian solution of 'Networks of Excellence' was proposed as opposed to 'Centers of Excellence.' A regional- or provincial-coordinated, patient-centered approach may be feasible. Patients could be diagnosed, treated, and followed locally in the community by urologists and oncologists, with care directed by the regional center. The development of a multidisciplinary forum with a coordinator would be key. All cases could be presented and discussed centrally through the MDT coordinator, with expert testis pathology and radiology review. This would support physicians in smaller centers to continue to manage certain predefined (clinical stage 1 or good-risk) patients locally. Metastatic intermediate-/poor-risk, salvage, or those requiring RPLND would ideally be treated at the designated regional center (Halifax for Atlantic Canada) and if not possible, at the designated provincial center.

Developments to improve the quality of care to patients who live remotely could include the development of virtual clinics. For example, Dr. Robert Hamilton is the principal investigator of a virtual clinic trial at the Princess Margaret Cancer Centre in which testicular cancer patients with clinical stage 1 disease are randomized to standard of care in-person visits or virtual assessments.<sup>35</sup> Patients in the virtual arm follow the standard Princess Margaret surveillance schedule, however, instead of an in-person clinic visit, they interact asynchronously with their physician through a custom-designed online module. The study is currently accruing, with a safety, feasibility, and cost metrics report planned out in two years.

There is concern that regionalization will further marginalize patients who live in remote locations. However, this is not supported by the evidence. For example, Lorie et al demonstrated no correlation between distance (>100 km from referral center) or community size and receipt of treatment modality in rectal cancer in British Columbia.<sup>36</sup> Similarly, Canale et al demonstrated no correlation between rurality and outcomes in advanced pancreatic cancer in British Columbia.<sup>37</sup> In bladder cancer, a multicenter study across the U.S. and Canada observed distance travelled to the treatment facility was not associated with 90-day mortality, cancer-specific or all-cause mortality<sup>38</sup> following cystec-

**Table 1. Population, surface area, and incidence of testis cancer**

	Population	Surface area	New cases per year	Incidence per 100 000
U.K.	66.04 million	242 495 km <sup>2</sup>	2400	3.6
Germany	82.79 million	357 386 km <sup>2</sup>	4020	4.9
Denmark	5.75 million	42 933 km <sup>2</sup>	300	5.2
Canada	37.06 million	9 985 000 km <sup>2</sup>	1100	2.7
U.S.	327.2 million	9 834 000 km <sup>2</sup>	9560	2.9

tomy. These studies suggest that the travel distance is not a barrier to appropriate oncological care at regional tertiary care centers.

No doubt the need to travel to a referral center adds a further burden to patients and their families. However, Shalowitz et al highlighted that 80% of patients are willing to travel to a referral center when made aware of the improved survival advantage in ovarian cancer.<sup>39</sup> Interestingly, Wong et al demonstrated that distance travelled was one of the least likely factors to influence a patient's preference regarding decisions for cancer care in Australia.<sup>40</sup> Resio et al demonstrated that the most common factor making patients reluctant to travel for treatment was the associated cost and that 94% would travel if the financial burden was adjusted (transport, parking, hotel); many of these associated costs are already accounted for in travel grants in Ontario and other provinces.<sup>41</sup>

From a physician's perspective, regionalization can result in drain of patients away from local practice, resulting in a reluctance of some community-based physicians to support it. Many physicians have managed testis cancer appropriately for many years and are reticent to give this up. The method of reimbursement for many surgeons and physicians in Canada (who are mostly private practitioners) is fee-for-service.<sup>42</sup> One suggested key element is to engage local providers in a testis cancer network. Not all patients need to be diverted to large tertiary referral centers. The initial diagnosis, staging, and radical orchiectomy can be offered locally in accordance with defined treatment pathways. The local providers can be involved with presenting their cases at the weekly MDT meeting. The MDT consensus can then offer a treatment strategy, which can, in some patients, be carried out locally. The 'Network of Excellence' model can be developed to engage local providers to direct and facilitate patient care.

## Conclusions

Care of testis cancer patients is often non-guideline-concordant; this is particularly true away from large-volume cancer centers. Such deviation from guidelines can translate into worse outcomes. The Canadian Testis Cancer Workshop participants agreed that a structured pathway for diagnosis and treatment of testis cancer patients is required. Several barriers to successful Canadian implementation of this were identified, with expansive geography being the most formidable. This prevents simply adopting systems that have been successful in other countries and/or healthcare systems.

A Canadian-specific approach to regionalization is required. We think the first step is to identify what the key performance indicators and quality metrics are to track the quality of care received. Efforts are ongoing within the Canadian testis cancer community to do this. After iden-

tifying these metrics, implementation of a 'Networks of Excellence' model, similar to that seen in sarcoma care, could be effective, coupled with increased use of health technology, such as virtual clinics and telemedicine. These changes are best implemented in stages, but it is clear change needs to happen.

**Competing interests:** Dr. Wood has been an advisory board member (with no compensation) for Astellas, Pfizer, and Novartis; and has participated in clinical trials supported by Aragon, AstraZeneca, BMS, Exelixis, Merck, Pfizer, and Roche. Dr. Rendon has been an advisory board and speakers' bureau member for, and has received honoraria from Abbvie, Amgen, Astellas, AstraZeneca, Bayer, Ferring, Jansen, and Sanofi. Dr. Kollmannsberger has been an advisory board member for Astellas, BMS, Novartis, Pfizer, and Sanofi; has received honoraria from BMS, Novartis, and Pfizer; and has participated in clinical trials supported by Astellas, AstraZeneca, BMS, Janssen, Merck, Novartis, Pfizer, and Sanofi. Dr. Jewett has been an advisory board member for Pfizer and Theralase Tech; has received honoraria from Olympus, Pfizer, and Theralase Tech; and holds investments in Theralase Tech. Dr. Chung has received honoraria from Sanofi and has participated in clinical trials supported by AbbVie. The remaining authors report no competing personal or financial interests related to this work.

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