The history of cryosurgery in Canada: A tale of two cities

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Abstract

Although not commonly available in Canada, cryosurgery (cryoablation) for prostate cancer has been practiced in many countries. The field of cryoablation has evolved significantly over the past 30 years. Two prostate cryoablation programs were started in Canada in the early 1990s, in London, ON and Calgary, AB, focusing, respectively, on salvage therapy following radiation failure and primary local treatment. This article chronicles the development of the two programs and outlines the scientific and clinical contributions by investigators at the two centers.

A brief history of time……in cryosurgery

Treatment of tumorous growths was first described centuries ago using a mixture of ice and various "medicinal salts." "Cryosurgery," or cryoablation, for the prostate was initially used for benign prostatic hyperplasia and subsequently extended to prostate cancer in the 1960s by Gonder and Soanes, and further explored by Flocks and Megalli in the early 1970s.[1-3] Initially, the prostate had to be exposed via a perineal incision, whereby a large probe as the source of below-freezing temperature (from a liquid nitrogen course) was directly applied to the prostatic surface. Unfortunately, acceptance of cryoablation as a prostate cancer treatment was significantly hindered by the high complication rate, mainly with urethro-rectal and urethra-cutaneous fistulae.[1-3] The main technical limitations were the lack of devices to accurately and reliably monitor placement of the cryo-probes and real-time control of the extent of tissue freezing.

Perfect storm for prostate cryoablation

A serendipitous "perfect storm" occurred in the early 1990s for cryoablation of internal organs. Firstly, transrectal ultrasound of the prostate was popularize by Lee et al to access the prostate with a transrectal probe, improving prostate imaging and biopsy.[4] This led to improved prostate imaging for precise cryoprobe placement and for intraoperative monitoring and control of the freezing process, avoiding excessive freezing and damage to vital adjacent structures, such as the rectum and bladder trigone. Secondly, endourological techniques for percutaneous renal stone treatment were pioneered by Smith and colleagues, paving the way for transperineal percutaneous access to the prostate with the Seldinger technique and tract

dilation for cryoprobe insertion. Percutaneous access helped minimize fistulous complications. Thirdly, improvements in cryogenics and better understanding of cryo-biology helped the transition from liquid nitrogen-based freezing to argon-based technology, which applies the Joule-Thompson effect. The later-generation cryo-systems allow more rapid freezing and slower thawing (optimizing the cytocidal effect) and the smaller-caliber cryoprobes or cryo-needles facilitated more accurate placement and treatment targeting.[5,6] Onik et al were first to use real-time transrectal ultrasound (TRUS) for precise probe placement, monitoring the ice-ball enlargement during treatment and visual protection of the rectum.[7] Other ancillary improvements in technology included thermal sensors strategically placed peri-prostatically, allowing better temperature monitoring, and urethral warming devices to better protect the urethra and minimize sloughing and subsequent strictures.[4,8,9] In this article, we chronicle the development of the first two prostate cancer cryoablation programs in Canada, one in Calgary, AB, initially focusing on primary therapy for lower-staged cancers, and one in London, ON, focusing on salvage cryoablation for radio-recurrent prostate cancer. We examine the impact of these two programs on prostate cancer patient care in Canada and their contributions to the urological literature.

Prostate cryoablation program in London, ON

Shortly after the initial presentation on primary prostate cancer cryoablation by Onik and Cohen, the prostate cancer cryosurgery program at University of Western Ontario (UWO, now Western University) in London, ON was launched. The first patient was a 66-year-old male with localized intermediate-risk prostate cancer and a relative contraindication for pelvic radiotherapy due to inflammatory bowel disease. His body mass index was 45. Primary cryoablation was felt to be a viable minimally invasive treatment, which was carried out in 1992. A crucial element of the successful program was the partnership with a radiologist with expertise in prostate ultrasound. Dr. Donal Downey was invaluable in the perioperative management and followup assessment of the cryoablation patients, including serial TRUS-guided biopsies.

Adding to the aforementioned "perfect storm" was the invention by a medical physicist, Dr. Aaron Fenster at the Robarts Research Institute in London, ON, of a three-dimensional ultrasound imaging system,[10,11] which was incorporated into the intraoperative algorithm for prostate cancer ablation. The "almost instantaneous" 3-D reconstruction software permitted intraoperative verification of accurate cryo-probe placement in the transverse, sagittal, and the previously unavailable coronal views of the prostate. This modification of TRUS- guided prostate cryoablation, published in 1998, was a "world-first."[11] It facilitated real-time confirmation of cryoprobe placement in 3-D and monitoring of the freezing process with views of the expanding ice-balls nearing the rectal wall. The added features should theoretically improve efficacy and reduce the morbidity of prostate cryoablation.

Traditionally, patients who experienced treatment failure following primary radiotherapy were reflexively and routinely placed on androgen deprivation therapy (ADT). This widespread practice might, at times, be premature or even inappropriate, as a significant proportion of such patients could be candidates for local salvage therapy, i.e., salvage prostatectomy or some form of salvage ablative therapy. To partly fulfill this unmet need, the decision was made at UWO to concentrate on treating patients who had localized histologically proven recurrence following primary radiotherapy.

A major contributor to the salvage cryoablation program at UWO was Dr. Juanita Crook, a radiation oncologist in Ottawa and, subsequently, in Toronto. Dr. Crook was investigating the time course of histological response to radiation seen in post-radiotherapy prostate biopsies. Dr. Crook and colleagues incorporated post-radiotherapy biopsies as early as 12–18 months into their followup algorithm and noted a significant proportion of patients with "early" post-radiotherapy positive biopsies did develop progressive disease. Although some were "indeterminant" and eventually resolved, others persisted and started to drive up the prostate-specific antigen (PSA).[12-14] Dr. Crook referred numerous patients to the UWO program for salvage cryoablation — patients diagnosed with localized persistent prostate cancer following radiotherapy, who otherwise might have waited much longer prior to a diagnosis of radio-recurrence, by which time the window of opportunity for cure might have been missed. Radiation oncologists from many other Canadian cancer centers and other urologists followed suit with their referrals.

The results on the initial 118 patients with median followup of 18.6 months (range 3–54) were published in 2001; Kaplan-Meier plots showed patients free of histological recurrence levelling at 87%.[15] Predictors of treatment failure included, as expected, high pre-cryoablation PSA level >10 ng/ml, high pre-radiotherapy Gleason score (≥8), and high pre-radiotherapy stage (≥T3). These results mirrored those by Drs. Pisters and von Eschenbach et al from MD Anderson Cancer Center, who reported a two-year biochemical recurrence (BCR)-free survival of 74% for pre-cryotherapy PSA <10 ng/ml compared to 28% for PSA >10 ng/ml.[16]

Serial prostate biopsy was part of the followup routine, regardless of biochemical or clinical response. This contributed to the understanding of the natural history of salvage cryoablation to the patterns of treatment failure, and to improved patient selection.[17] UWO was a key member of a consortium of several North American cryosurgery centers that designed a pretreatment nomogram predicting biochemical failure after salvage cryoablation for locally recurrent prostate cancer.[18]

With a prospectively maintained database and longer followup on a larger cohort of 187 patients at UWO, durable responses were noted; with median followup of 117 months, the BCR-free rate at 10 years was 35%, with an overall survival (OS) rate of 76%.[17,19,20] Further update on the cohort of 187 patients, with median followup now very mature at 149 months, 12-year OS was 56%, while cancer-specific survival (CSS) was reported at 81%.[21] Again, pre-radiation Gleason score and grade, pre-radiation T stage, and pre-cryoablation PSA levels were found to be predictors of CSS. Another parameter, PSA nadir post-cryoablation, was found to be prognostic. Importantly, 49% of the patients had not required ADT, and for those who did progress onto requiring ADT, there was a clinically meaningful delay of median 101 months from time of cryoablation to commencement of ADT.[22] There are ongoing collaborative efforts with other institutions that have comparable large and mature databases (Mayo Clinic, Memorial Sloan Kettering Cancer Centre) on salvage radical prostatectomy. The combined analyses have contributed to the knowledge and guidance for management of radio-recurrent prostate cancer.[23,24] Notably, when compared to patients without further local therapy after radiation recurrence, there has been improvement in CSS and OS associated with salvage local therapy.[25]

Randomized trial on advanced-staged prostate cancer at UWO in London, ON: Primary cryoablation vs. external beam radiotherapy

In addition to the salvage cryoablation program, in mid-2000, a randomized trial on locally advanced prostate cancer comparing the relative efficacy of primary cryoablation vs. primary radiotherapy was conducted at UWO. Patients with cT2C, cT3A, and cT3B were randomized to either primary whole gland cryoablation or external beam radiotherapy (EBRT) (standard dose was 66 Gy), with both groups receiving three months of ADT prior to and three months following their prostate intervention.

Shortly after the inception of this trial, however, there was a global major paradigm shift in the radiotherapy management for prostate cancer at high-risk for metastasis. Firstly, Bolla et al published preliminary results of a European Organization for Research and Treatment of Cancer (EORTC) randomized trial with EBRT and three years of adjuvant ADT vs. no ADT. The ADT group had significantly better disease-free survival and OS.[26-28] Secondly, there had been increasing evidence of therapeutic benefits of dose escalation for patients undergoing EBRT compared to the "conventional" dose (≤68 Gy).[29,30] These two developments suggested the radiotherapy arm of the UWO randomized trial provided suboptimal treatment. Accrual to the trial drastically decreased and the trial was stopped with enrolment of only 62 patients out of the original target of 144.[31] Deficiencies in numbers and trial design notwithstanding, with long-term followup, disease-specific survival and OS were comparable between the groups. However, the eight-year biochemical disease-free survival rate was significantly lower in the cryoablation group (17.4% vs. 59.1%, p=0.01).[32] Cryoablation may be more suited for less bulky prostate cancer. Longer duration neoadjuvant hormonal therapy or a multimodal approach should improve biochemical disease-free survival in this patient population. This trial was one of the first attempts worldwide in comparing two interventional modalities for prostate cancer in a randomized setting. The other such randomized trial, led by Dr. B. Donnelly, was taking place contemporaneously across the country 3000 km away in Calgary, AB.[33]

Primary prostate cryoablation program in Calgary, AB

In 1993, cryoablation as a treatment for localized prostate cancer was presented at a meeting of the genitourinary committee of the Radiation Therapy Oncology Group (RTOG) and appeared interesting. Coincidentally, at that time, there was a program in place to treat liver metastases with cryoablation at Tom Baker Hospital in Calgary. This program was run by Dr John Saliken, an interventional radiologist. We got together with Dr. Saliken with a view to exploring the role of cryoablation in patients with localized prostate cancer. A proposal for a phase 2 pilot study was submitted to the Alberta Cancer Board, who agreed to fund a pilot of 30 cases, on condition that there was no surgical fee.

Patients were invited to participate in a prospective, non-randomized pilot study of the safety and efficacy of cryosurgery in treating localized prostate cancer. Recruitment began in December 1994 and closed in February 1998. All patients had histologically proven adenocarcinoma of the prostate, with PSA readings <30 ng/mL (Hybritech). All patients had negative bone scans. If the risk of lymph node involvement exceeded 5%, as calculated by the formula of Roach, laparoscopic pelvic lymph node dissection (PLND) was carried out prior to inclusion in the study.[34] It was explained to all patients that radical prostatectomy and radiotherapy are the standard treatment choices and that cryoablation was, at the time, an investigational modality.

The objective of this study was to assess the safety and short-term results of this treatment, with a view to conducting a phase 3 randomized trial comparing cryoablation with EBRT in localized prostate cancer. Accrual of the phase 2 pilot study went very well, but we were unwilling to begin the phase 3 randomized trial until we had three-year results on at least 30 cases, so the work continued; eventually, 76 patients were treated, with 11 patients receiving a repeat treatment.[35-37] A single freeze/thaw cycle was used in the first 10 cases, changing to two freeze/thaw cycles from case 11 onwards, which was becoming the standard procedure. The five-year OS and CSS rates are 89% (95% confidence interval [CI] 83–97%) and 98.6% (95% CI 96–100), respec-

tively. The undetectable PSA rate (≤0.3 ng/mL) for low-risk patients (13) was 60% at five years, moderate-risk (23) 77%, and high-risk (40) 48%. PSA <1.0 ng/mL at five years is 75%, 89%, and 76%, respectively.[36] At this point, it was felt appropriate to proceed to the phase 3 randomized trial.

Alberta Cancer Board agreed to fund the work, (with the same stipulation of no surgical fee) and further funding was obtained from National Cancer Institute of Canada. A multidisciplinary team was set up comprised of urology, interventional radiology, radiation oncology, medical oncology, and biostatistics. Patient eligibility was similar to the pilot, with one significant difference that PSA was <20 ng/ml (rather than <30 ng/ml). Clinical bulky T3 cases were not eligible. Accrual to this type of trial was very difficult, so eligible patients and their significant others were invited to small group presentations of all information. The presenters were a urologist, a radiation oncologist, and a medical oncologist. Out of 627 eligible patients, 244 (38%) agreed to randomization, which was a very high accrual rate. The study ran from December 1997 to February 2003 and was closed prematurely due to slowing accrual. All patients received neoadjuvant hormones in both arms, as this was standard radiotherapy practice at the time. All patients who were randomized to the radiotherapy arm were treated with a standard four-field box technique (2 Gy daily, five days per week) using high-energy megavoltage (MV) X-rays of 10 MV. The prescribed radiation dose was 68 Gy. The dose was increased to 70 Gy in early 2000 and finally to 73.5 Gy in late 2002 in response to changing standards of practice. The results at 100-month followup essentially showed that both treatments had similar outcomes.[33,38] This trial and the one on locally advanced disease by Chin et al[31] remain two of the earliest randomized trials worldwide in prostate cancer comparing different interventional modalities.

Dr John Robinson, a clinical psychologist with the program, published several notable articles on the quality of life outcomes of the patients who had undergone either primary or salvage cryoablation.[38-40] Drs. Rewcastle, Muldrew, and Baissolov conducted much laboratory work on the biomechanics of cryoablation, resulting in multiple publications and presentations.[41-44] With the significant contributions by the Calgary program in primary cryoablation, Dr. Donnelly was a major contributor on the "Best practice statement on cryosurgery for the treatment of localized prostate cancer" issued by the American Urological Association in 2008.[45]

Salvage cryoablation program in Calgary, AB

A salvage cryoablation phase 2 trial was also initiated Tom Baker Hospital in Calgary in 1998 to treat radio-recurrent prostate cancer patients. Selection criteria were strict: biopsy-proven residual cancer in the prostate, negative metastatic workup, PSA doubling time >1 year, PSA <20 ng/ml. Forty-six patients were treated. Using the PSA definitions for biochemical failure as PSA <0.3 ng/ml, 51% and 44% were considered disease-free at one and two years, respectively.[39,46] There was one patient with a recto-prostatic fistula. On the basis of these results, salvage cryoablation was (and still is) offered to suitable patients in Calgary. We have modified our patient eligibility is accordance with the work of Dr. Chin and colleagues showing that the best results are achieved with PSA <5 ng/ml in the recurrent patient.

Cryoablation continues to be available in Calgary (and Edmonton), both as a primary and salvage treatment for suitable patients. In the primary setting, there are many patients who are not suitable for either surgery or radiation, and this provides a good option for such cases. Furthermore, many patients live long distances from a radiotherapy facility (some from outside of Alberta), thus making many weeks of treatment difficult. For these men, cryoablation is a viable option, with only an overnight stay, and in some cases, same-day discharge is an option. The risk of fistula formation was held up as an objection to this treatment, but in the primary cases, this should not be a concern in competent hands. Erectile dysfunction is universal initially with whole-gland ablation, but approximately 30% of men resume sexual activity, similar to the number following EBRT in our prospective trial.

In the salvage setting, as noted earlier from the UWO experience, most salvageable men are not offered this local treatment, and instead are only offered ADT, with the attendant morbidities. As we have shown, a substantial proportion of these cases could be potentially salvaged by local ablation therapy, either cryoablation or high-intensity focused ultrasound, obviating or deferring ADT.

Conclusions

The two parallel prostate cryosurgery programs in Canada both started in 1990s — one focusing initially on primary ablation and one concentrating in salvage ablation for radio-recurrent disease — have had a combined output of over 50 peer-reviewed publications. They have made contributions to improved understanding of cryobiology and technical advances of prostate cryoablation, as well as to cryosurgery-related issues of imaging and histopathology. More importantly, clinical information, such as patient selection, prognostication, quality of life issues, and the role of cryoablation in the entire spectrum of prostate cancer management, has benefited worldwide from the experience and lessons learned via these two Canadian programs. This "tale of two cities" on the history of prostate cryoablation in Canada, unlike the "Tale" by Charles Dickens, appears to have had a favorable outcome.

Competing interests: Dr. Chin has been an advisory board member for and received payment from Abbvie, Astellas, Janssen, Profound Medical Inc., Sanofi-Aventis, and Tersera; and has been a clinical

trial consultant for and received honoraria from Profound Medical Inc. Dr. Nair has received payment from Profound Medical Inc. for participating in a user feasibility study. The remaining authors report no competing personal or financial interests related to this work.

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