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# Current practice in total-body irradiation: results of a Canada-wide survey

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## ABSTRACT

**Background** Total-body irradiation (TBI) is used to condition patients before bone marrow transplant. A variety of TBI treatment strategies have been described and implemented, but no consensus on best practice has been reached. We report on the results of a survey created to assess the current state of TBI delivery in Canada.

**Results** A 19-question survey was distributed to 49 radiation oncology programs in Canada. Responses were received from 20 centres, including 12 centres that perform TBI. A variety of TBI dose prescriptions was reported, although 12 Gy in 6 fractions was used in 11 of the 12 centres performing TBI. Half of the centres also reported using a dose prescription unique to their facility.

Most centres use an extended-distance parallel-opposed-pair technique, with the patient standing or lying on a stretcher against a wall. Others translate the patient under the beam, sweep the beam over the patient, or use a more complicated multi-field technique. All but 1 centre indicated that they attenuate the lung dose; only 3 centres indicated attenuating the dose for other organs at risk.

The survey also highlighted the considerable resources used for TBI, including extra staff, prolonged planning and treatment times, and use of locally developed hardware or software.

**Conclusions** At transplant centres, TBI is commonly used, but there is no commonly accepted approach to planning and treatment delivery. The important discrepancies in practice between centres in Canada creates an opportunity to prompt more discussion and collaboration between centres, improving consistency and uniformity of practice.

**Key Words** Total-body irradiation, TBI, radiotherapy

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## INTRODUCTION

Total-body irradiation (TBI) is a treatment that is frequently used as a conditioning strategy to eliminate malignant cells and prevent graft rejection in advance of hematopoietic stem-cell transplantation[1–3]. Although chemotherapy is usually the primary method of conditioning, TBI has certain advantages. It does not spare sanctuary sites such as the central nervous system and the testes, and it does not depend on the blood supply for heterogeneous delivery[3–6].

The prescription dose for TBI can depend on the disease, the patient's condition, and the type of transplant. Initial experience using TBI was based on single-fraction treatments, frequently using 10 Gy[7]. Experiments later demonstrated survival advantages for fractionated treatment, specifically to reduce toxicity. The most common prescription used in TBI is 12 Gy in 6 fractions, delivered twice daily[8].

Total-body irradiation can have substantial complications. Early effects can include, but are not limited to, nausea and emesis, and late effects can include interstitial pneumonitis[9–11]. It has been questioned whether the dose rate substantially affects the side effects associated with treatment, because some studies have suggested a link between high dose rates and toxicity, and others have indicated no such relationship[12–15].

Total-body irradiation can be delivered on dedicated units specifically designed for the technique—such as the GammaBeam 500 (Best Theratronics, Kanata, ON)—or a modified conventional treatment unit. For practical reasons, including the relatively low volume of TBI treatments, the most desired approach is to make use of a treatment unit that will still be available for general use. However, at their nominal treatment distances, most conventional treatment units are limited to field sizes much smaller than the length of a human body. To overcome that limitation,

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patients are generally placed at an extended distance away from the source and are treated supine and prone, or left and right, using a parallel opposed pair (POP) technique[16,17]. Other options include sweeping a beam across the patient or translating the patient through the beam[18–20]. Treatment delivery has traditionally used simple open fields, although modulated deliveries using tomotherapy and volumetric modulated arc therapy are also being used[21–23].

The relatively small number of TBI patients treated in a population and the various resources available at each centre have resulted in a high degree of variation in how TBI is prescribed and delivered[1,24]. That variation was illustrated in a survey of 56 TBI centres across Europe, the Mideast, and Australia, which found "extremely heterogeneous" treatment design and clinical practice, with no two centres giving identical answers about their treatments[25]. Such differences create obstacles to clinical trials and to consistent quality care across jurisdictions.

The purpose of the present study was to assess how consistently TBI was being performed across Canada, a geographically large nation with a low population density and a relatively small radiation medicine community. It was expected that the survey would reveal differences in technique similar to those seen in the European study, but with more similarities in approach because of the smaller community.

## METHODS

A 19-question survey focusing on radiation prescription, delivery technique, and resources for TBI was created. A few questions were added for centres wanting to report no delivery of TBI. The survey was programmed at the Web site https://www.SoGoSurvey.com/. Anticipating a wide variety of answers, most of the questions asked for free-text answers, allowing the users to be as descriptive as they had to be. The survey was circulated to 49 heads of clinical medical physics departments across Canada. Responses were gathered from November 2015 to February 2016. Centres that were known to deliver TBI were actively recruited to respond.

Between November 2015 and February 2016, 20 centres responded to the survey, with 12 reporting that they supported a TBI program. At least 1 response was received from every Canadian province.

## RESULTS

### Technique and Prescription

Table I summarizes the prescriptions and treatment techniques used in the 12 Canadian centres that reported delivering TBI. The descriptions used in the table are simplifications of the survey answers. For example, the 7 survey respondents that reported using POP techniques revealed notable differences in how the TBI was carried out, including variations in the degrees of compensation for tissue thickness and in the position of the patient. The "Other" column in the table indicates a dose prescription unique to the particular centre.

Although no question on the survey asked responders to indicate the prescription that was used most frequently at their centre, 2 centres clearly indicated that that a prescription other than 12 Gy in 6 fractions was most commonly used at their centre. At those centres, the most frequently used prescriptions were 6.5 Gy in 1 fraction and 4 Gy in 2 fractions.

Table II sets out dose rates and sparing of organs at risk. The identification numbers used to identify centres are consistent for all tables. Centre 8 did not provide information about dose rate, other than the rate varied considerably because of their delivery method (volumetric modulated arc therapy).

Two centres indicated that they used $^{60}$Co treatment units to deliver TBI, although they used the units in different ways: one used a sweeping beam from a swivelling gantry; the other used an extended POP technique.

Table III indicates the equipment used for the planning and delivery of TBI.

### Resource Requirements

Table IV sets out the TBI resources required by the centres, providing information on the number of patients treated and the time involved in planning and delivering the treatments. Also indicated are the additional staff whose presence was required for treatment delivery. The table suggests that about 400 patients are treated with TBI in Canada each year. Most patients are treated at 2 specific cancer centres, one in Ontario and the other in Alberta. When the patients were stratified by province instead of by centre and normalized to the provincial population[26], as shown in Figure 1, a median of 11.7 patients were treated per million population. The maximum number of patients treated in one province, Alberta, was 29.9 patients per million population.

Another resource concern was what happens in the case of equipment breakdown. Most centres indicated they would treat on an equivalent unit, but the 2 centres using $^{60}$Co indicated that they did not have that option. One centre reported that their backup plan was an extended POP treatment on a linear accelerator; the other reported that they had no alternative plan.

### Other Information

All centres delivering TBI indicated that they planned to continue to deliver TBI in the future, although 3 reported that they were considering changing their technique.

Of the 8 centres that reported not delivering TBI, only 1 expressed an interest in delivering TBI in the future. Those 8 centres—located in Ontario, Quebec, and Atlantic Canada—indicated that they refer their patients to Halifax, Toronto, Montreal, or Ottawa.

## DISCUSSION

Our survey provides a snapshot of TBI practice across Canada—information that has not been presented in the literature until now. It highlights that, although there are some consistencies in practice, including a predisposition to use 12 Gy in 6 fractions as the prescription dose, there are many inconsistencies as well: from the technique used, to the reduction of the dose to the lungs, and to the time and staff resources required for the technique. One of the

**TABLE I** Total-body irradiation treatment techniques and dose–fractionation schemes used across Canada

| Centre | Technique | Dose (Gy)/fractions (*n*) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 12/6 | 2/1 | 4/2 | 3/1 | 5/1 | 13.5/8 | Other |
| 1 | Translating bed | √ | √ | √ | √ | √ | — | √ |
| 2 | Extended POP | √ | √ | — | — | — | — | — |
| 3 | Extended POP | √ | √ | √ | — | — | — | — |
| 4 | Extended POP | √ | √ | √ | — | — | √ | √ |
| 5 | Extended POP | √ | √ | √ | — | √ | — | — |
| 6 | Extended POP | — | — | — | √ | — | — | √ |
| 7 | Extended POP | √ | √ | √ | — | — | — | √ |
| 8 | VMAT-TMI | √ | — | — | — | — | — | — |
| 9 | Junctioned plans | √ | √ | √ | — | — | — | √ |
| 10 | Sweeping beam | √ | — | — | — | — | √ | √ |
| 11 | Extended POP | √ | √ | — | — | √ | — | — |
| 12 | Translating bed | √ | — | — | — | — | — | — |

POP = parallel opposed pair technique; VMAT = volumetric modulated arc therapy; TMI = total marrow irradiation.

**TABLE II** Midline dose rates and organ-at-risk (OAR) shielding used across Canada

| Centre | Dose rate (cGy/min) | Shielding | |
|---|---|---|---|
| | | Lung | Other OARs |
| 1 | 51 | 12 Gy | Kidneys: 12 Gy |
| 2 | Average 9, maximum 12 | "Yes" | Not indicated |
| 3 | 15.5 | 9 Gy | Not indicated |
| 4 | 14.1 | "Depends on Rx" | Not indicated |
| 5 | 11.6–15.4 | None | Not indicated |
| 6 | 16 | 8 Gy | Not indicated |
| 7 | 20 | 50% Rx | Not indicated |
| 8 | VMAT | 60% Rx | Liver: 60% Rx; heart: 60% Rx |
| 9 | 20–50 | Approx. 80% Rx | Not indicated |
| 10 | 18–20 | 10 Gy | Not indicated |
| 11 | 14 | 103% Rx | Not indicated |
| 12 | 50 | 8 Gy | Kidneys: 10 Gy; Liver: 10 Gy |

Rx = prescription; VMAT = volumetric modulated arc therapy.

**TABLE III** Extra equipment associated with total-body irradiation treatment planning and delivery

| Centre | Use commercial planning system? | Use in-house equipment? | *In vivo* dosimetry (accepted accuracy, %) |
|---|---|---|---|
| 1 | √ | √ | MOSFET (10) |
| 2 | — | √ | TLD (10) |
| 3 | — | √ | MOSFET (3) |
| 4 | √ | √ | None |
| 5 | — | √ | Semiconductor (20) |
| 6 | — | — | Ion chamber and OSLD (10) |
| 7 | √ | — | Ion chamber (5) |
| 8 | √ | — | None |
| 9 | √ | √ | MOSFET (+5/–10) |
| 10 | — | √ | Semiconductor (2) |
| 11 | — | √ | TLD (10) |
| 12 | √ | √ | Ion chamber (5) |

MOSFET = metal oxide–semiconductor field-effect transistor; TLD = thermoluminescent dosimeter; OSLD = optically stimulated luminescence detector.

clearest examples is found for the 2 centres that use the translating bed technique. Despite the fact that both deliver 12 Gy in 6 fractions, and both use a similar dose rate and the same fundamental delivery technique, one compensates the lung dose to 12 Gy, while the other compensates to 8 Gy. Additionally, one shields the kidneys and liver and also undertakes electron compensation to make up for chest wall dose reduction because of lung shielding.

The implications of the reported variation are considerable. The ability to undertake a clinical trial or even to compare TBI outcomes from centre to centre would likely be greatly confounded by differences in the independent options.

Our survey revealed that most Canadian centres work frequently with the 12 Gy in 6 fractions pattern. However, the wide range of supplemental prescriptions indicates that, although radiation oncologists might have reached a consensus, variability also remains. Worldwide, TBI fractionation varies considerably and is influenced by chemotherapy, irradiation regimes, the conditioning protocol used, and resources available. Those factors also likely explain the variations seen between the Canadian centres.

The inclusion of a total marrow irradiation technique in place of TBI at 1 centre is interesting. That techniques

**TABLE IV** Resources required for total-body irradiation treatment

| Centre | Patients treated in preceding year (*n*) | Planning time | Treatment time | Extra staff |
|---|---|---|---|---|
| 1 | 20 | 4 Hours | 1.25 Hours | Medical physicist |
| 2 | 20 | 1 Hour | 1 Hour | None |
| 3 | 25 | 2 Hours | 1 Hour | Medical physicist |
| 4 | 10 | Several hours | >1 Hour | Medical physicist, extra therapists |
| 5 | 109 | 1.25 Hours | 30–45 Minutes | Extra therapists |
| 6 | 4 | 4 Hours | 2.5 Hours | Radiation oncologist, medical physicist, extra therapists |
| 7 | 12 | 3 Days | 1 Hour | Radiation oncologist, medical physicist, extra therapists |
| 8 | 12 | 4 Weeks | 2 Hours | None |
| 9 | 119 | 2 Days | 1 Hour | Medical physicist |
| 10 | 50 | 1–2 Hours | 1–1.5 Hours | Medical physicist |
| 11 | 9 | 3–4 Hours | 45 Minutes | None |
| 12 | 12 | 8–10 Hours | 1 Hour | Medical physicist |

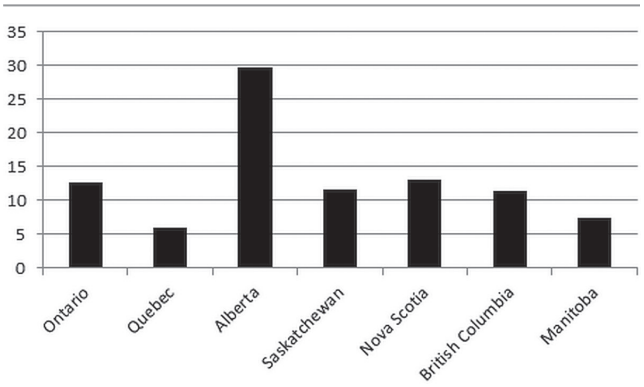


**FIGURE 1** Number of total-body irradiation patients treated annually, by province, per million residents.

is, of course, different. In some diseases, the desire is to treat not just the bone marrow, but also the circulating blood, which contains residual cancer cells. Additionally one of the benefits of TBI is that radiation can reach areas such as the central nervous system and testes, where most chemotherapy regimens are ineffective. Dose reduction beyond the bone marrow will reduce side effects, but can also affect outcome. The balance between treating and sparing tissue is not clear and is most evidenced in the high degree of variability in the lung dose across the country.

The example of the total marrow irradiation technique highlights the importance of dose rate. Traditionally, the dose rate has been limited because of concerns that high dose rates might cause additional toxicity. Multiple treatment centres throughout the world are now using intensity-modulated radiotherapy techniques, which do not have any restrictions on dose rate, and also some modernized variations of traditional techniques. Overall, the survey indicated that, aside from the centre using volumetric modulated arc therapy, Canadian centres avoid high-dose-rate treatment, although it should be noted that multiple centres reported a higher dose rate than was reported in a recent European survey (which reported a maximum of 37.5 cGy/min)[25].

The predominant use of 4 Gy in 2 fractions at 1 centre in Alberta is a result of their practice to use a reduced-intensity conditioning regimen for their transplants[27]. That regimen allows for a broader range of patients to undergo the treatment[28], which could in part explain why the patients treated per population rate is so much higher in Alberta than in the other provinces, even though the neighbouring provinces from which the Alberta centre would receive referrals have treatment rates comparable to those in the rest of Canada. Other Canadian jurisdictions should take note, because if clinicians have a desire to implement reduced-intensity conditioning regimens elsewhere, the number of TBI patients treated and the resources required for the program could potentially increase substantially.

The resources involved in TBI treatments vary considerably across Canada, although the survey highlights the resource-intensive nature of the treatment. Even the fastest delivery technique reported requires two 20-minute patient bookings, and the twice-daily nature of the treatment doubles the amount of time required on the linear accelerator. Other resources include the routine use of *in vivo* dosimetry and the requirement for additional staff to be present at the treatment unit. As an extreme example, centre 6 (Table I) indicated that it takes 2 days to plan each patient. Given that the centre treats about 120 patients annually, almost 1 full time employee is required to do nothing other than plan TBI patients at that centre.

Of the centres that indicated they were pursuing modifications to their technique, 3 reported having recently developed arc techniques similar to the one presented in papers by Hudson *et al.*[29] and Evans *et al.*[30]. However, they worked independently of each other because of variations in equipment and treatment approach. That situation seems to indicate that treatment differences in TBI throughout Canada will persist into the future.

## Limitations

Our study has the standard limitations of survey research. The overall response rate was only 41%, and although there is reason to believe that all centres delivering TBI responded

based on referral patterns, it is possible that 1 or 2 TBI treatment centres could have been missed. Free text was allowed to be used for most questions so that responders could elaborate on their answers, but that approach also allowed for some ambiguous answers to be fed into the survey. In addition, the survey represents a 3-month window of time, and changes in the TBI approach will have occurred before publication of the present article.

## CONCLUSIONS

Throughout Canada, TBI practices vary substantially, with no two centres delivering the same combination of prescription, organs-at-risk shielding, and treatment technique, making it challenging to compare clinical outcomes. The community would benefit from more active collaboration between centres and results comparisons at national radiation oncology and medical physics conferences, with the goal of moving toward a more uniform best practice.

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### CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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