

## Scientific Article

# Total Body Irradiation and Total Skin Irradiation Techniques in Belgium and the Netherlands: Current Clinical Practice



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## Abstract

**Purpose:** In 2014, a Belgian/Dutch Nederlandse Commissie voor Stralingsdosimetrie (NCS) task group was formed to develop guidelines on the clinical practice of total body irradiation (TBI) and total skin irradiation (TSI).

**Methods and Materials:** As a basis for these guidelines, a survey conducted among 17 Belgian and Dutch radiation oncology institutions measured the clinical practice of TBI. Four of these institutions also performed TSI. An update was performed in 2019 and 2020 because several institutions innovated their TBI techniques.

**Results:** As old and more recent studies have shown, clinical protocols for TBI and TSI still vary considerably between institutions.

**Conclusions:** New radiation therapy technologies have been introduced relatively slowly for TBI purposes.

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## Introduction

Total body irradiation (TBI) and total skin irradiation (TSI) have been practiced for over a century and since about last midcentury, respectively. After Dessauer and Eifer practiced TBI in 1905 and 1907,<sup>1,2</sup> many others followed.<sup>3,4</sup> Despite the long-term clinical practice and experience, TBI techniques were already shown 3 decades ago to vary significantly between Europe and Japan.<sup>5,6</sup> Quast argued that survival rates depend primarily on indication and staging, but that variations in treatment techniques may also play a role.<sup>5</sup>

In the past 30 years techniques have not converged as multiple, recent publications have shown. Studinski et al. showed that for TBI no commonly accepted planning and

treatment delivery exist.<sup>7</sup> Similar findings have been published recently in Japanese, European-Middle East, Australian, and American studies.<sup>8-14</sup> TSI is much less performed clinically but, again, multiple approaches exist in treatment techniques.<sup>15</sup>

By applying newer hard- and software, cutting-edge techniques for TBI were developed. Some of these techniques (e.g., volumetric modulated arc therapy [VMAT]-based techniques) are already used clinically.<sup>16-19</sup> Other potential techniques are helical tomotherapy,<sup>20-25</sup> proton therapy,<sup>4</sup> radio-immunotherapy,<sup>26</sup> or more complex VMAT techniques, including couch rotations and high-precision delineations of multiple structures once logistics have been optimized.<sup>27,28</sup>

In 2014, the NCS committee formed a Belgian/Dutch task group to develop guidelines on the clinical practice of TBI and TSI, employing a survey held among Belgian and Dutch radiation therapy institutions. An update was performed in 2020 because several institutions had innovated their TBI techniques.

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Compared with recently published surveys, more detailed questions about TBI were included and (to our knowledge, for the first time) TSI was surveyed as well. The results are presented and discussed in this report.

## Methods and Materials

A survey was performed electronically by all Dutch and Belgian radiation oncology institutions in 2014. The survey consisted of 5 general, 49 TBI-related, and 38 TSI-related questions. According to the Dutch cancer registry, the incidence of hematological malignancies in the Netherlands was 9540 in 2018, with approximately 310 TBI treatments annually.<sup>29</sup> Belgian registries reported incidences of approximately 6500 malignancies and 136 TBI treatments annually.<sup>30</sup> The Netherlands reported 15 (incidence of mycosis fungoides: 100/year; 17 million inhabitants) and Belgium 11 (incidence 47/year; 10.4 million inhabitants) annual TSI treatments in the questionnaire.

Data were processed electronically and wherever necessary, responders were encouraged to respond in detail. Our goal of a 100% response rate to get a complete overview of the clinical practice regarding TBI and TSI in the Netherlands and Belgium was met. The results shown in this report represent the status of 2020.

## Results

All 21 Dutch radiation oncology institutions responded. In total, 9 Dutch institutions practice TBI, including all 8 university centers. Only 1 (university) institution practices TSI. In total, 10 Belgian institutions responded, of which 8 (including 7 academic institutions) practice TBI. Three of the (university) centers that perform TBI also perform TSI.

The results from both countries are grouped unless indicated otherwise. Because the survey was not always fully completed by every single institution, the statistics were processed and are quoted accordingly (i.e., number of institutions may vary over the answered questions).

### Total body irradiation results

Per annum, on average 26 TBI patients are treated per institution (average: 25; range, 1-70) for all dose schemes (Fig. 1). The reported dose-fractionation schemes show a large variety in total dose and fractionation strategy (Table 1). For non-ablative treatments,  $1 \times 2$  Gy and  $2 \times 2$  Gy regimens are mostly applied, and for ablative treatments a  $6 \times 2$  Gy regimen is common.

Eleven of 17 institutions have dedicated TBI teams to perform treatments. Twelve institutions schedule patients similar to other patient groups (i.e., regularly throughout

the day). Two institutions schedule patients at the beginning and 3 at the end of a day.

Fifteen of 17 institutions have a designated backup machine. Two of these 15 machines are available at another (nearby) hospital such that a patient can be treated there on the same day. The other 2 institutions have no backup facility.

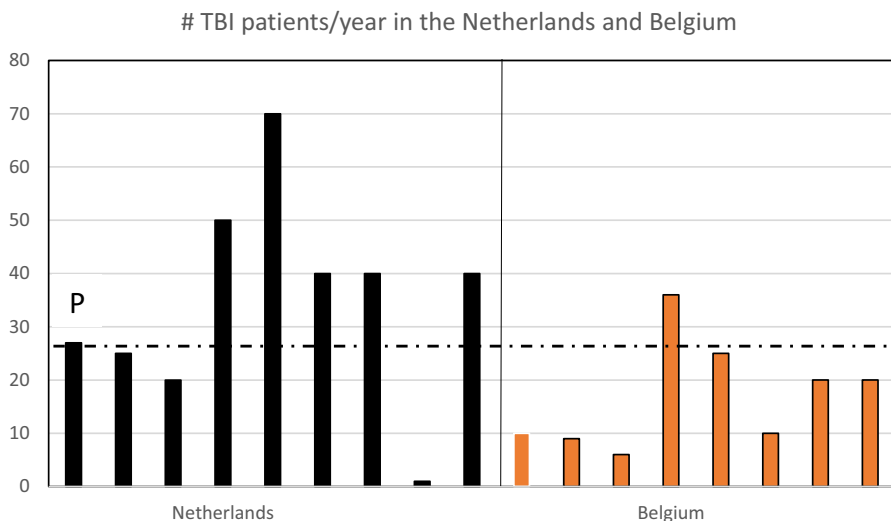
Eleven of 15 institutions perform manual monitor unit (MU) calculations, occasionally using tabulated values. The other 4 perform dose calculations based on computed tomography (CT) information in 2015, but this number increased to 6 in 2020. Several institutions expect to perform treatment planning based on CT information within the next few years, partly depending on replacements of their treatment planning system.

Most institutions ( $n = 11$ ) position the patient in a lateral decubitus position on an extended surface skin distance, varying from 3.7 to 5.5 m. This requires a dedicated separate treatment couch. Other positioning methods used are the standing/leaning position ( $n = 2$ ) or allowing the patient to sit on a chair ( $n = 3$ ). Lateral positioning on the couch is commonly done using a vacuum mattress, chin to chest, drawn up knees, one arm along a side and the other arm supporting the head. Special attention has to be paid to extremity positioning for patient comfort and dose homogeneity.

Currently, 11 institutions use a 2-field technique with patients in the lateral decubitus position. In all but one institution, the treatment couch is rotated  $180^\circ$  in between fields, and the remaining institution alternates the patient's side position per treatment session. The other institutions use 4 or 5 beams, and 4 of these institutions use field-in-field techniques to get a more homogeneous dose distribution. Beam energies vary from 6 MV to 23 MV (Table 2).

The most frequently used treatment dose specification point is midplane in the patient, either in a single point at, for example, the level of the umbilicus ( $n = 10$ ) or averaged over multiple midline points ( $n = 3$ ). Two institutions use full CT planning and therefore employ the body dose–volume histogram for dose specification. Thirteen institutions reported their dose rate, which was on average 20 cGy/minute (range, 4-40 cGy/minute).

Critical organs (e.g., lungs, eyes, and kidneys) are shielded from irradiation in various institutions, depending on the fractionation used. In general, for a total dose  $>6$  Gy, shielding of organs at risk (e.g., lungs) may be considered. Lung shielding is performed in 11 of 17 institutions, 9 institutions shield lungs with individualized Cerrobend blocks, the other 2 institutions use a multileaf collimator (MLC). The eyes are shielded individually in 1 institution and standardized in 4 institutions. Furthermore, 1 institution also blocks both kidneys individually, 1 institution uses Lucite plates to reduce the dose to the head if exceeding, for example, 110% of the prescribed



**Figure 1** Number of total body irradiation patients treated annually in the Netherlands (black bars) and Belgium (red bars). Each bar represents an institution. Average value indicates average number of total body irradiation patients annually for both countries. *P*, dedicated pediatric treatment center.

**Table 1** Reported dose-fractionation schemes for both ablative and nonablative total body irradiation treatments in the Netherlands and Belgium

|                     |       |       |       |           |       |          |       |       |         |
|---------------------|-------|-------|-------|-----------|-------|----------|-------|-------|---------|
| Fractionation, Gy   | 1 × 2 | 1 × 8 | 1 × 9 | 2 × 2     | 2 × 2 | 2 × 4.5  | 2 × 5 | 2 × 6 | 3 × 3.3 |
| Fractions per day   | 1     | 1     | 1     | 1         | 2     | 1        | 1     | 1     | 1       |
| No. of institutions | 11    | 1     | 1     | 6         | 3     | 1        | 1     | 1     | 2       |
| Fractionation, Gy   |       | 3 × 4 | 4 × 2 | 5 × 2     | 5 × 2 | 6 × 1.67 | 6 × 2 | 6 × 2 | 8 × 1.5 |
| Fractions per day   |       | 1     | 1     | 2 × 2 & 1 | 1     | 2        | 1     | 2     | 1       |
| No. of institutions |       | 1     | 1     | 1         | 1     | 1        | 1     | 8     | 1       |

dose, and 1 institution also shields the ankles and knees to improve dose homogeneity. Two institutions do not use any shielding.

All but 3 institutions use Cerrobend blocks attached to a spoiler screen with double-sided tape, 2 institutions use MLC, and 1 uses an in-house developed system with a screw/nut fixation. Block positioning is mostly verified with the naked eye, and 4 institutions use a dedicated mobile imager with a charge-coupled device detector to acquire MV images (Theraview).<sup>31</sup>

Responses to the pretreatment quality assurance (QA) questions were received from 17 institutions, of which 11 rely on standard QA (i.e., no extra measurements other than for non-TBI treatments). In addition, 3 institutions perform annual output measurements at TBI treatment distance. Patient QA is mostly performed by in vivo dosimetry with either diodes, mosfets, or similar tools (7 institutions) or thermoluminescent dosimeters (2 institutions) performed at least at the umbilicus and in few institutions also at other body positions, such as the head, lungs, or abdomen. Tolerance levels were mentioned by institutions and vary from 3% to 10% of the prescribed dose (mostly 5%).

**Table 2** Beam qualities used for total body irradiation in all institutes

| Beam energy | Number of institutes |
|-------------|----------------------|
| 6 MV        | 4                    |
| 10 MV       | 5                    |
| 15 MV       | 5                    |
| 18 MV       | 2                    |
| 23 MV       | 1                    |

Seven of 17 institutions use American Association of Physicists in Medicine report 17 on TBI as a reference, and the 10 other institutions combine local experience with various scientific papers.<sup>32</sup> For hygienic precaution measures, personnel at 7 institutions wear masks and gloves, in 7 departments treatment couches are disinfected, and personnel at 4 institutions use protective clothing. In 2 other institutions, standard hospital hygiene measures, including hand disinfection, are applied, and in 4 institutions no special precautions are taken. The regimen depends on whether or not ablative fractionations are applied.

As part of their clinical implementation of TBI, only 4 institutions have performed a risk analysis. Three

institutions followed Healthcare Failure Mode and Effect procedures, and the remaining one provided no further information about the adopted method.<sup>33,34</sup>

### Total skin irradiation results

TSI is mostly used to treat mycosis fungoides and occasionally skin lymphomas. The applied protocol is described in American Association of Physicists in Medicine report 23 (Stanford technique).<sup>35,36</sup> The yearly average number of patients is 11 in Belgium and 15 in the Netherlands (Fig. 2). Fractionation schemes vary between  $8 \times 1.5$  Gy on a daily basis and  $7$  to  $10 \times 3$  Gy every other day.

Three of 4 institutions have a dedicated team for TSI treatments and the same 3 institutions also have a backup machine on site. All 4 institutions schedule their TSI patients on a regular basis (i.e., not at a specific timeslot).

All 4 institutions adopted the Stanford technique, treating the patient in the standing position (2 institutions) or lying on a stretcher (2 institutions) in a prone and supine position.<sup>35,36</sup> Patient positioning is verified using visual markings and/or light field. The Stanford technique uses 6 positions, and additional fields to the crown, armpits, perineum, soles of the feet, and (in case of women) the mammary fold if needed, additional treatment fields were given based on in vivo dosimetry performed at the first fraction. Electron energy varies from 4 MeV to 6 or 9 MeV, with the latter 2 in combination with a Lucite diffuser to increase surface dose and prevent serious complications due to treatment of too large volumes.

Two institutions use simplified treatment planning with standard fields and tabulated MUs to account for patient geometry differences. One institution employs standard

fields and MUs that have been verified as a standard class solution with no patient specific corrections. The fourth institution uses MUs that are based on solid water phantom measurements of the percentage depth dose and in vivo dosimetry at the first fraction.

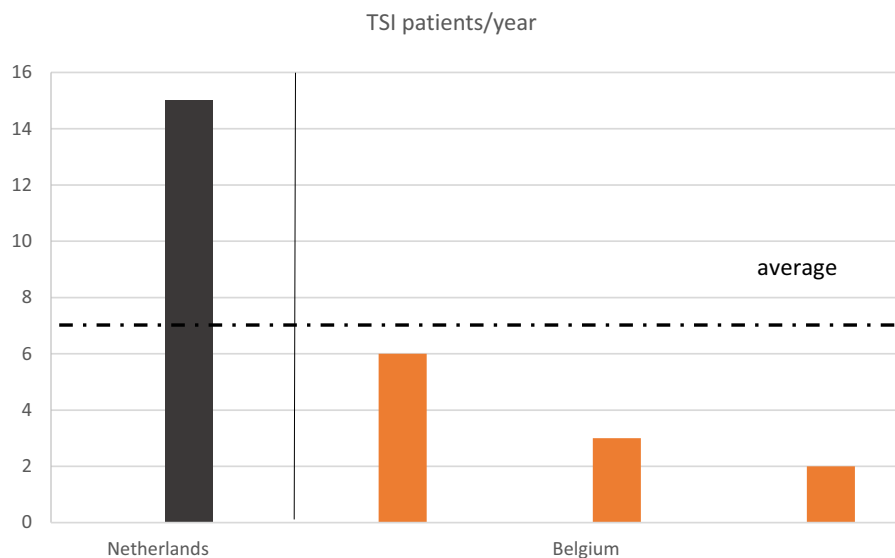
In 3 institutions, the determined MUs and machine parameters are manually entered into the record-and-verify system, and the fourth institution uses their system to import standard plans from the treatment planning system. Three institutions rely on the standard machine QA whereas 1 institution periodically measures the dose in a phantom at treatment distance.

EBT gafchromic film is used at 2 institutions for in vivo dosimetry at about 10 anatomic locations, allowing for a maximum dose deviation of 10%. A possible solution when exceeding the threshold is adjustment of the gaps between the separate fields. During treatment, the eyes are shielded using lead goggles in 3 institutions, and the fourth institution does not use shielding (but also uses the lowest dose scheme).

Two facilities have a backup machine on site, 1 facility has a backup stored elsewhere, and another has no backup. Of note, TSI may be postponed because this treatment is not time-critical, in contrast to TBI. Dose calculations are table-based and performed manually, and the maximum-allowed dose inhomogeneity is between 10% and 20%. All institutions verify patient positioning visually. No risk analysis was performed before the clinical introduction of TSI techniques.

### Discussion

Although TBI has been practiced in radiation therapy since the beginning of the previous century, many



**Figure 2** Number of total skin irradiation patients treated annually in the Netherlands and Belgium. Average value indicates average number of total skin irradiation patients annually for both countries.

variations exist among practices even within countries, as shown in various surveys.<sup>1,4,5,9,10,37</sup> Our survey in Belgium and the Netherlands is not only more detailed than previous surveys (100% response rate), but also includes TSI. Additional recommendations to existing guidelines are made for centers that want to optimize their techniques or perhaps start with TBI and/or TSI.<sup>38,39</sup>

Notwithstanding that Belgium and the Netherlands are small countries with not many institutions that practice TBI (n = 19) or TSI (n = 4), the applied techniques and procedures vary considerably concerning patient setup and shielding of critical organs, but also in terms of fractionation schemes and using dedicated teams or scheduling patients. Therefore, the variety in TBI treatment techniques within Europe as observed by Quast<sup>5</sup> and other more recent surveys still holds for the current survey.

Although we did not distinguish pediatric TBI treatments, this group deserves special attention (TSI is not applied for this group in Belgium and the Netherlands). Hoeben et al. describe a European survey and conclude that “there is a high uniformity in fractionation and in lung shielding” and that institutions are increasingly implementing new CT-based techniques.<sup>40</sup> Also, “a radiation therapy working group will be established to define international guidelines for pediatric TBI.”<sup>40</sup> In the Netherlands, all pediatric patients are referred to one dedicated institution (Fig. 1; approximately 25 patients/year). In Belgium, pediatric patients are treated at multiple institutions in low numbers.

In contrast to Japan, where almost 20% of 186 institutions use moving couch techniques,<sup>8,9</sup> Belgian and Dutch institutions apply large source-surface distances. In addition, the most common patient positioning in Japan is supine (>70%), sometimes combined with anterior–posterior/posterior–anterior field configuration and a short source-surface distance.

Most large centers use a dose rate <15 cGy/minute. Only 7 centers go up to 26 cGy/minute. In Japan, 80% of centers shield the lungs and almost 60% also shield the eye lenses (vs 65% and 31%, respectively, in our survey).

In our survey, lung shields consisted mainly of Cerrobend blocks (almost 75%). No specific timeslots were scheduled but due to long treatment times, TBI is performed during times when other radiation therapy types are not scheduled (46%) or is limited to 1 fraction per day (7%) or the number of TBI treatments is limited (20%).

Today, a risk analysis is performed (sometimes compulsory) as part of the clinical implementation of a treatment technique. Although not yet demanded by law, in the Netherlands, a covenant, Medical Technology, has been developed in the medical technology community that prescribes risk analyses included in periodically held national audits.<sup>41</sup> However, this was not common or demanded in the past. Techniques established long ago are generally not based on a risk analysis, although

occasionally a retrospective risk analysis is performed. An essential aspect of the risk analysis involves the level of expertise and experience (e.g., dedicated team), where a minimum of 5 annual treatments should be maintained to have guaranteed expertise.<sup>11</sup> Therefore, a minimum of 5 annual treatments are recommended, preferably in a single center rather than distributed over multiple centers.

If the time interval between treatments is high (e.g., >3 months), then a dry run (chain test) is recommended. One institution explicitly indicated that although a backup machine is available on site, a recalculation of the MUs to be delivered was needed owing to different beam quality. A risk analysis would have shown that having identical machines, beams, and treatment room sizes is ideal to prevent recalculations in an otherwise possible stressful situation. This is especially the case if a backup machine is available at a different (but nearby) institution, as 1 responder indicated. For comparison, in Canada, all but 2 facilities had an identical backup machine.<sup>7</sup>

The survey showed that 11 of 17 institutions have a dedicated TBI team, and 3 of 4 have a dedicated TSI team. Ideally, a dedicated team is deployed to perform TBI and/or TSI. From a resource perspective, such treatments could be most efficiently scheduled on predefined timeslots. The efficiency of scheduling also strongly depends on the workload of the team involved, especially if multiple fractions are given on the same day.<sup>11</sup> Other existing surveys did not mention data on timeslots. In this survey, 11 of 17 institutions schedule TBI treatments similarly as other non-TBI treatments, and 5 institutions schedule patients at the beginning or end of the working day. For TSI treatments, all 4 institutions schedule patients as a regular treatment.

Discussions on the survey results in the work group have already led to local adaptations of TBI techniques. For example, one institution treated patients for multiple decades with a dose rate of approximately 15 cGy per minute, but based on experiences by others and the literature, the dose rate was recently increased to its maximum (40 cGy/minute).<sup>42–44</sup> However, there is no clear consensus in the literature regarding this subject. Using a higher dose rate is an improvement from both an economic point of view and regarding patient comfort, because they may minimize the need to reposition patients during treatment. Recently, imaging possibilities have become available to verify the positioning of patients.<sup>31,45</sup> Three participating institutes have purchased such a system and more are considering doing so. User experiences still need to be published. Another institution adopted CT information for dose calculations.

Altogether, the survey has led to reviews and occasionally reconsiderations of local treatment techniques. Clear and more converging treatment techniques would also be beneficial for clinical outcome comparisons. A recent American survey among 101 institutions showed that none of the institutions uses MLC in their TBI



technique and only 28% of the responders perform treatment planning based on CT information.<sup>14</sup> Four of 15 responders used CT information, which is a similar ratio as in the United States. The recent survey update shows that the number of institutions that use CT has increased to 6 (40%).

Most centers in Belgium and the Netherlands practice lateral decubitus position, which increases homogeneity when using parallel-opposed pair treatment fields. However, not all patients found lying on their arm to be comfortable for the duration of the treatment.<sup>46</sup> Peters et al. concluded that supine or combined supine–prone positioning is found to be the most comfortable despite the fact that dose inhomogeneity will be increased.<sup>47</sup> In contrast, Quast recommends anterior–posterior/posterior–anterior TBI rather than bilateral TBI fields, which cause a low dose in the mediastinum, ribs, and arms, although the latter can reduce the lung dose.<sup>2</sup> However, modern imaging techniques before treatment, 3-dimensional treatment planning systems, and dose verification systems are currently available to improve dose homogeneity irrespective of the treatment technique.

## Conclusions

As discussed, the clinical implementation of advanced technologies (e.g., CT, VMAT, and MLC) for TBI purposes goes relatively slow. Nevertheless, high advanced and complex technologies are studied in detail.<sup>48,49</sup> However, logistics, workflow, and treatment times remain a challenge<sup>27,28</sup> as also found by several institutions involved in this survey. On the other hand, high-dose schemes might require more complex treatment techniques to spare organs at risk. However, this also depends on the expected clinical relevance. Finally, guidelines to practice TBI hopefully will lead to more and more converging treatment techniques.<sup>39,40,50</sup>

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