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REVIEW ARTICLE

Beyond cancer treatment – a review of total lymphoid irradiation for heart and lung transplant recipients

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Abstract

Immunosuppressive drugs used in the management of heart and lung transplants have a large monetary and quality of life cost due to their side effects. Total lymphoid irradiation (TLI) is one method of minimising the need for or replacing post-operative immunosuppressive drugs. A literature review was conducted on electronic databases using defined search terms. The aim was to establish the indications for the use of TLI, its advantages and disadvantages and the weaknesses associated with the methods used in related research. Eight articles were located that focused on TLI usage in combating organ rejection. These studies identified that the use of TLI resulted in a reduction in early rejection. One study reported a drop in rejection episodes from 0.46 to 0.14 episodes per patient per month once the TLI was complete. While the short-term prognosis is excellent, the long-term outlook is less positive with an increased risk of organ rejection and myelodysplasia 3.5 years post-TLI. This review reminds us that radiation therapy (RT) is not exclusively indicated for cancer treatment. While TLI cannot replace immunosuppressive drug therapy, it can offer a treatment option for people that cannot tolerate immuno-suppressive drugs, or when conventional anti-rejection treatment is no longer viable. Reported long-term complications suggest that TLI should be used with caution. However, this modality should not be overlooked in cases of chronic rejection. Further research is required to establish the efficacy of RT in the treatment of transplant patients who are unsuitable for drug-based anti-rejection therapies.

Introduction

Radiation therapy (RT) is an effective strategy in the treatment of cancer, both in a curative and palliative role. However, this is not the extent of its therapeutic use. RT can be used for numerous non-malignant conditions, including acoustic neuroma and the prevention of keloid scar growth or heterotopic ossification just to name a few. While lesser known, and much less common, RT has also been used in the management of post-transplant organ rejection. While immunosuppressive drugs are the gold standard to both stop organ rejection and combat rejection episodes, it is possible for patients to build up a resistance to this medication. It is in these cases that RT offers a novel treatment option.

Organ transplantation

Disease, injury, congenital or genetic problems can result in an organ such as the heart, lung, liver or kidney to fail. While there are often medical procedures and pharmaceuticals that can temporarily maintain the function of these failing organs, the only way to correct the problem is an organ transplant. On 1 January 2012 there were approximately 1500 Australians on the organ transplant waiting list.[1] Transplanted organs are donated by other members of the society; the donation can be after death or a living donation.[1] Except in rare cases where the organ comes from an identical twin, the organ is genetically different and thus will be viewed as 'foreign' by the recipient's immune system.[2,3] This leads to organ

rejection, which is the destruction of an organ due to the recipient's immune system attacking the 'foreign' body.[3] While there is historical evidence in Christian texts that organ transplantation was attempted in the middle ages, the first medically documented case of human to human transplantation was in 1936 when Yurii Voronoy transplanted a kidney in an attempt to save a patient from renal failure, however the patient died 36 h later.[4] Sir Peter Midber and René Kuss' work led to the understanding of organ rejection and in 1954 David Hume demonstrated that rejection did not occur if transplantation was between identical twins.[4]

Organ rejection is mediated by the immune system and there are three distinct types, which are related to the signs and symptoms observed:

1 Hyper-acute rejection is common in cardiac transplants but a rare condition with lung transplants, with only five cases being medically documented as of 2008.[5] This type of rejection is aggressive and initiated by the pre-existing humoral immunity, which are antibodies that react to 'foreign' matter. Macroscopically, characterisation includes gross oedema and cyanosis of the graft.[5] This type of organ rejection is often lethal within 4–48 h post-transplant.[5]
2 Acute rejection is most prevalent 3–6 months post-surgery and due to either T-cell attack or the formation of specific antibodies which act against the organ.[6] This type of rejection can be managed by increasing the dose of the immunosuppressive drugs. Acute rejection is often seen in episodes, where it is unlikely that a single episode will lead to failure of the newly implanted organ.[6]
3 Chronic rejection occurs when there is long-term loss of function from the transplanted organ. The hallmarks of this type of rejection are scarring of internal blood vessels and other similar structures within the organ.[7] This type of rejection is seen months or years after surgery with the patient often requiring a new organ.[7]

In the 1980s cyclosporine (CyA), the first 'immunosuppressive drug' became available.[8] CyA therapy revolutionised organ transplantation survival rates to 86% (first year) and 78% (5 years).[8,9] Further research and development produced azathioprine (AZA) and then a host of other immunosuppressive drugs, however these drugs are not without their side effects (see Table 1).[8,10]

The use of RT in total lymphoid irradiation

Total lymphoid irradiation (TLI) was the treatment of choice for Hodgkin's lymphoma before cytotoxic chemotherapy in the 1960s. This technique focused on the whole of the lymphatic system with a view to destroying the cancer cells within it.[13] The immunosuppressive nature of TLI is well documented, in particular, the reduction in the T-cell population.[13–15] Thus, this technique has been used to stop or limit

Table 1. Common immunotherapy anti-rejection drugs and their side effects.[11,12]

Anti-rejection drug	Side effects
Calcineurin inhibitors such as cyclosporine Calcineurin inhibitor that binds to the cyclophilin in the cytoplasm. This causes a failure to transcribe a variety of factors required to activate T cells and target cells.	Urinary tract infections and nephrotoxicity.
Azathioprine Acts as a pro-drug for mercaptopurine, which strongly affects proliferating T and B cells. This is due to mercaptopurine inhibiting an enzyme essential to DNA synthesis.	Nausea, vomiting, dizziness, diarrhoea, fatigue, skin rashes, hair loss, anaemia and increased susceptibility to infections.
Muromonab-CD3 – OKT 3 An antibody that binds to T cells causing de-activation. Can be used to treat rejection episodes as well as prevent them.	Fever, tachycardia, myalgia, pulmonary oedema nausea, hypotension, diarrhoea, nephrotoxicity and neurotoxicity that may lead to aseptic meningitis and seizures.
IL-2 receptor antagonists – basiliximab and daclizumab An antibody that binds to the α subunit of the T cell and thus stops it from proliferating.	Generally well tolerated. Gastrointestinal upset and increased susceptibility to bacterial and viral infections.
Prednisone Is a corticosteroid – it binds to the glucocorticoid receptors in the cytoplasm, impairing the action of lymphocytes, monocytes and macrophages.	Susceptibility to infection, osteoporosis, impaired wound healing, fluid retention, aseptic necrosis of bone, cataracts, hyperlipidemia, obesity, glucose intolerance, hypertension gastric ulcers, polyphagia and mental health problems such as insomnia, emotional liability, manic and depressive psychosis.

rejection[14] because the radiation affects the DNA of these cells, they are unable to divide quickly after being activated and the immune reaction is compromised.[2] While there is slight variation in TLI techniques, a common method is outlined in Table 2. Due to the success of CyA and the other immunosuppressive drugs, TLI for use in minimising the possibility of organ rejection is less well known. However, there is still research being undertaken on the effectiveness of this therapy.[14,16,17] Investigation into this area is uncommon compared to other more main stream areas of RT research.

Aim

This review aims to investigate the role of TLI in limiting organ rejection after heart and lung transplants. It will also clarify the specific indications for the use of TLI. The benefits and contraindications to using TLI in organ rejection management will be discussed. The authors will also discuss methodological issues inherent in researching topics that are not main stream.

Method

The literature review carried out for this article was undertaken exclusively via electronic resources, initially in October 2012, with a subsequent search in 2013. All articles used were sourced from the following free full text or open access databases: CINAHL, BiomedCentral, Pubmed Central and the licensed database Science Direct accessed via the Monash University library. Initial keyword and Boolean phrase searches used were: TLI and radiation, transplant and irradiation and heart, transplant and irradiation and lung, radiotherapy and transplant, RT and transplant. Duplicates were removed and the remaining abstracts reviewed for relevance to the topic. Articles published prior to 1995 were excluded as this year is a RT milestone that signifies the introduction of dose painting and sculpting and functional imaging.[22]

Table 2. Radiation therapy technique and prescription from the reviewed articles.[13,14,16–21]

Element	Description
Number of fields	3 – mantle, para-aortic and inverted Y
Energy	6 MV, 10 MV if separation is extremely large (>22 cm)
Beam set up	AP-PA (anterior posterior–posterior anterior)
Total dose	8 Gy*
Dose/fraction	0.8 Gy
Fraction/week	2

*Keogh et al.[19] prescribed dose was 6.4 Gy over eight fractions.

The clinical implementation of dose painting and functional imaging resulted in more conformal treatment techniques. It should however be noted that the data collection periods for some of the articles were prior to 1995. Articles concerning TLI for organ transplants other than the heart or lung were also excluded because they were outside the scope of this review. All remaining articles describing the use of TLI to treat or limit organ rejection were included in this review ($N = 8$).

Results

Indications for the use of TLI

The articles reviewed suggested that TLI was indicated for one of two conditions; bronchiolitis obliterans syndrome (BOS) (three studies) and cardiac rejection (five studies). BOS is a non-reversible obstructive lung disease caused by compression of the bronchioles. This life-threatening compression is due to both fibrosis (scar tissue) and inflammation. BOS is caused by an immune reaction to either micro-organisms or the lung itself in transplant cases. A heart transplant is an established and effective means of combatting end-stage heart failure. Rejection of the donor heart is definitively diagnosed by a cardiac biopsy. A patient suffering from cardiac rejection will have decreased organ function and thus, this is a life-threatening situation. Reported numbers of TLI participants in the articles selected varied widely, ranging from 6 to 66.[13,16] Three of the articles compared a TLI trial group to a control group (no irradiation) with the size of these groups ranging from 5 to 122 participants.[13,16]

TLI prescription and technique

All studies undertaken except Salter et al.[20] delivered a total dose of 8 Gy, in 0.8 Gy fractions, with the remaining study giving a dose in the range of 2.4–8.4 Gy. The data from the eight articles examined in this review have been collated and can be seen in Table 3.

Completion of the TLI treatment course

All studies reported much lower numbers of participants completing the TLI treatment course compared to those who were prescribed this treatment. The reasons for treatment to be delayed or abbreviated were neutropenia, thrombocytopenia, infection (bacterial and viral), unrelated medical conditions or increase in symptoms such as progressive pulmonary decline.[14,18] Most of the studies monitored the blood cell levels of the participants. When certain criteria were met, such as CD4+

Table 3. Overview of the eight articles reviewed in total lymphoid irradiation (TLI).

Study	Patient study size	Gender	Age range (average age)	Treatment rationale	TLI dose	Patients who received entire prescribed dose	Average time before first rejection episode	Rejection episodes before TLI (average)	Rejection episodes after TLI (average)	Reported deaths
Diamond et al.[14]	11	10 Male 1 Female	15–51 (33)	BOS refractory to conventional treatment	0.8 Gy fx 8 Gy total	4	18.6 months	Not stated	Not stated	6
Verleden et al.[16]										
TLI group	6	3 Male 3 Female	23–41 (32)	BOS no longer responding to azithromycin	0.8 Gy fx 8 Gy total	Not stated	11 months	Not stated	Not stated	3
Control group	5	Not stated	23–54 (38)		No dose	No dose	Not stated	Not stated	Not stated	1
Ghadja et al.[175]	7	4 Male 3 Female	19–62 (46)	RCCAR endomyocardial biopsies	0.8 Gy fx 8 Gy total	2	33 months	5.9 per patient	1.7 per patient	1
Salter et al.[20]										
TLI group	47	37 Male 10 Female	9–64 (48)	early or recurrent cardiac rejection after immune suppressive drugs therapy	Range 2.4–8.4 Gy	47	1–72 months majority 1–3 months	1.43 episodes/ patient/ month	0.10 episodes/ patient/ month	7
Control group received a heart transplant same centre and time frame but no TLI treatment	88	Not stated	Not stated		No dose	No dose	Not stated	Not stated	Not stated	NA
Keogh et al.[19]										
TLI group	7	Male	51–63 (Not stated)	Repetitive cardiac rejection episodes biopsy proven	0.8 Gy fx 8 Gy total	7	Within 4 weeks of transplant	3.4 ± 0.8 rejection episodes	0.1 ± 0.4 rejection episodes	0
Tacrolimus group	6	Male	53–62 (Not stated)	Grade 3A	No dose	6		3.2 ± 0.4 rejection episodes	0.7 ± 0.8 rejection episodes	0
Tallaj et al.[13]										
TLI group	66	Not stated	Not stated	RCCAR endomyocardial biopsies	0.8 Gy fx 8 Gy total	55	Not stated	16 episodes per year	6 episodes per year	3
Control group	122	Not stated	Not stated		NO dose	No dose	Not stated	Not stated	Not stated	Not stated
Wolden et al.[18]										
TLI group	47	34 Males 13 Females	1–64 (48)	Persistent, intractable cardiac rejection	0.8 Gy fx 8 Gy total	36	Not stated	0.46 episodes/ patient/ month	0.14 episodes/ patient/ month	20
Prophylactic group TLI given before a rejection episode	10	Not stated	Not stated		0.8 Gy fx 8 Gy total	Cancelled due to high rejection rate during the treatment	NA	NA	NA	4
Fisher et al.[21]										
TLI group	37	16 Male 21 Female	Not stated (38)	Progressive BOS	0.8 Gy fx 8 Gy total	27 (completed 80% fx)	NA	NA	NA	28

BOS, bronchiolitis obliterans syndrome; RCCAR, recalcitrant cellular cardiac allograft rejection; fx, fraction; TLI, total lymphoid irradiation.

lymphocyte count <100/mm^3, complete WBC <2000/mm^3, platelet count <100,000/mm^3, continuation with the prescribed treatment was re-assessed. Patients either had a break until the blood count returned to normal or treatment was stopped prematurely.

Effectiveness of TLI in the management of BOS

In 1998, Diamond et al.[14] described the treatment of 11 patients with chronic rejection of a lung transplant involving BOS with TLI.[14] Pulmonary function values and a complete blood count were used to rate the effectiveness of TLI. The overall success of this study was poor with 7 of the 11 transplants failing within 8 weeks post-irradiation. Subsequent to the treatment, six of the seven patients died, the seventh patient received a further transplant.[14] In this study, only 4 of the 11 patients finished the complete course of TLI. Reasons for premature termination of treatment included persistent thrombocytopenia, progressive pulmonary and worsening pulmonary infection. The study also reported that there were four patients who continued to display a positive response 24–72 weeks post-irradiation,[14] however it was not clear if the four patients whom completed the TLI course were also the four patients that experienced a positive outcome 24–72 weeks post-irradiation.[14]

Later in 2009 Verleden et al.[16] also investigated the management of BOS. The six patients within this study were not responding to the standard BOS treatment of azithromycin.[16] These patients were compared using *t*-test and analysis of variance (ANOVA) to a historical control group of five patients whom also did not respond to azithromycin.[16] Forced expiratory volume in one second (FEV_1) was used to measure the efficacy of the treatment. The TLI group FEV_1 did not improve post-irradiation but the decline was slowed (221–94 mL/mo; $P = 0.02$).[16] The control group's FEV_1 change was reported to be not significant (209–193 mL/mo; $P = 0.02$). Thus while the FEV_1 did not improve post-irradiation, the decline was slowed. This is likely due to the TLI limiting biological activities such as inflammation or cellular oedema seen in chronic rejection, which in turn allows the organ to perform better. As such, an increase in lung function is seen as a decrease in loss of FEV_1. However due to the scarring of the blood vessel and other damage TLI is unable to restore complete function.

A study by Fisher et al.[21] also demonstrated that TLI had the ability to significantly decrease the rate of decline in FEV_1 in lung recipients that were suffering from BOS.[21] This study consisted of 37 patients from a single centre over a 12-year period. The mean rate of decline was 97.5 mL/mo.[21] Fisher et al.[21] supported the use of TLI and recommended that this treatment should be used more widely. The authors also recommended that the optimal timing for TLI in the treatment of acute BOS should be investigated further.[21]

Despite these encouraging results, the long-term outcomes were not positive with seven patient's rejection issues returning within 8 weeks post-treatment and three deaths within 26 months post-TLI. These results appear to suggest that TLI cannot be used as a standalone strategy for managing organ rejection. However, it should be noted that two patients from the Verleden et al.[16] study and one patient from the Diamond et al.[14] study lived long enough to receive a secondary transplant and it therefore appears that TLI does have a role to play in the treatment of organ rejection.

Effectiveness of TLI in the management of cardiac rejection

In 1997, Wolden et al.[18] reported the long-term results of TLI as a treatment of cardiac rejection and the viability of its use as a prophylactic treatment. This study used historical data from 47 patients (37 intractable rejection, 10 prophylactic) between 1986 and 1995. Although the data from this study were acquired more than 20 years ago, the study meets the inclusion criteria (published articles from 1995 to present). Despite the age of the data, this article continues to be one of the prominent papers in this field and therefore justifies its inclusion in this review.

Wolden et al.[18] reported the participants who were suffering from cardiac rejection reduced from 0.46 episodes per patient per month to 0.14 episodes per patient per month.[18] However the prophylactic arm of the study was terminated due to the increase in cardiac rejection episodes. Diamond et al.[14] demonstrated a number of patients (56%) either stopped the TLI course early or undertook a break due to medical concerns. The intractable rejection patients' TLI resulted in a variety of positive outcomes; rejection rates dropped from 0.46 to 0.14 episodes per patient per month ($P < 0.0001$) and it decreased the need for Prednisone and had no increase in the occurrence of infection.[18] However, two patients developed malignancy, the outcome of which was not discussed.

TLI was shown by both Ghadjar et al.[17] and Salter et al.[20] to be an effective means of treating recalcitrant cellular cardiac rejection (RCCAR).[17,20] As with the previous Wolden et al.[18] article, data from both of these articles was also collected prior to 1995. However, their dates of publication met the inclusion criteria and their outcomes remain pertinent to the analysis and have therefore been included in the review. Ghadjar et al.[17] investigated the effects of TLI on seven patients with

RCCAR. They found that TLI was a useful strategy in RCCAR patients that experienced significant side effects of immunosuppressive drugs.[17] Salter et al.[20] also concluded that TLI was safe, effective and suitable as an adjunct treatment for early or recurrent cardiac rejection.

In 2001, a randomised trial compared Tacrolimus (FK506), an antibiotic with immunosuppressant action, to TLI for the control of repetitive rejection after cardiac transplantation.[19] The 13 patients within this study were on a regime of CyA, AZA, and prednisolone but were still experiencing episodes of rejection.[19] Seven participants were treated with TLI while the remaining six were given a 0.05 to 0.15 mg/kg per day of Tacrolimus. The TLI group grade 3A rejections (moderate rejection, some myocardial damage evident) went from 3.4 to 0.1 after treatment while the grade 1B (mild rejection, interstitial infiltration of lymphocytes) or lower rejections increased from 49% to 97%. A similar result was seen with the Tacrolimus group grade 3A rejection decreasing from 3.2 to 0.7 after treatment with grade 1B or lower increasing from 46% to 90%.[19] Keogh et al.[19] concluded that Tacrolimus and TLI are equally viable strategies to combat repetitive early rejection however within 3 years, five of the six patients receiving Tacrolimus had developed tumours (three malignant, two benign) compared with one person in the TLI group that developed prostate carcinoma. Thus, further research is required before the ubiquitous use of Tacrolimus as an adjunct treatment for organ rejection.

The study undertaken by Tallaj et al.[13] in 2011 is the most recent and had a larger sample size (66 TLI patients). It compared four groups (completed course of TLI, partial course of TLI, no TLI with high risk of rejection and no TLI with lower risk of rejection). This study was conducted over 18 years, allowing long-term side effects to be evaluated.[13] The results published by Tallaj et al.[13] are consistent with other studies by Wolden et al.,[18] Ghadjar et al.[17] and Salter et al.[20] that TLI reduced the hazard of rejection episodes for approximately 1 to 3.5 years. However Tallaj et al.[13] report that long-term effects of TLI were increased risk of rejection which is a new phenomena that had not been reported previously in studies with long-term follow up (7–10 years)[19] and therefore requires further investigation.

Limitations of Current Studies

Organ rejection is a serious and continual threat to all transplant recipients. While TLI is not a suitable replacement for anti-rejection drugs, it has been utilised effectively as an adjunctive therapy in selected cases.[13,17,20] Establishing the effectiveness of TLI to manage organ rejection is complicated. The full impact, both positive and negative, of TLI on organ rejection cannot conclusively be determined by simply analysing the studies included in this review.

Limited number of recent publications

One major barrier to being able to conclusively determine the suitability of TLI on organ rejection is the lack of published literature on this topic. This is most likely due to the use of TLI in organ transplant rejection being an uncommon RT procedure with very small numbers of patients being treated. This review only retrieved eight relevant articles via electronic resources, very few of these articles appeared in radiation oncology-/radiotherapy-specific journals. Older articles would often be excluded from reviews such as this due to concerns about validity and ability to obtain them in an electronic format. While some of the studies include data that were obtained before 1995, the authors believe that although there will have been technological advances since the study was conducted, the results of this study are still valid and worthy of inclusion, especially in the absence of more recent literature.

Participant selection

The results reported in the literature cannot be generalised to the entire population of transplant patients due to multiple variables, including the use of small patient sample sizes, heterogeneous patient characteristics, the primary inclusion of patients who were already experiencing organ rejection and the impractical and unethical nature of limiting treatment choices to a group of patients in order to complete a more rigorous randomised control trial. As an example, all the patients treated with TLI in the study conducted by Verleden et al.[16] had developed BOS and were no longer responding to Azithromycin. From a scientific view point, ideally these six patients should have been separated into two groups, one group receiving the TLI treatment and the other group would be the control, thus allowing a direct comparison to be made. This of course is unethical and not a valid option, thus, to alleviate this, a historical control group was used.

Sample size

Sample size is very important as it affects the integrity of the statistics generated from the research undertaken. While bigger is better, it is not practical or viable to conduct clinical research involving hundreds of patients due to practical and financial reasons.[23] Out of all the articles reviewed, the sample sizes were above five (TLI and control). Whilst these small sample sizes are unlikely to demonstrate statistical significance without

completing a meta-analysis on the combined results, the articles with smaller sample sizes seem to confirm the results of the studies with larger patient numbers. However, poor reporting of patient demographics such as age, gender and race makes comparison of trials difficult. One of the main issues in the articles was that they did not report whether or not the course of RT was completed. All studies examined mentioned either breaks or failure to complete the TLI, but none of the studies adequately outlined which patients had breaks or early cessation. Diamond et al.[14] reported four positive outcomes and that four patients finished their course of RT, however it was not disclosed if these four were the same people, therefore it is impossible to establish if partial TLI treatment negatively impact on the patients outcome.

Future Directions

The majority of authors are medical practitioners whose experience and interest focussed on the medical outcomes of the transplant and not the TLI itself. As noted earlier, the majority of the literature on this topic is published in non-radiation oncology journals. As such, the RT aspects of these studies may not have undergone the same level of peer review when reporting technical aspects of TLI. Publication of future studies would be enhanced with the input of radiation therapists as a 'new set of eyes' would offer insight and improved reporting of the multiple variables associated with RT that could potentially affect the results. Accurate reporting of TLI protocols would be more likely if RT staff were included as collaborators in TLI research, due to the specialised nature of RT. It is speculated that these improvements in reporting would also enable easier comparison of the results of future studies.

From the studies reviewed, there are no established guidelines for 'positive' outcomes in patients receiving TLI and the only universal 'negative' outcome is death. Each study defined its own positive outcome (i.e. rejection episodes, FEV or cardiac output after TLI) but the reporting of negative outcomes were less well defined, with patient death being the only consistently reported negative outcome. Negative outcomes are vital to compare and contrast studies such as rejection relapses. The collection of data relating to the number of patients that fail to complete the TLI RT course and the reasons for this, together with information on rejection episodes pre-/post-TLI and the RT side effects would assist both doctors and the patients in deciding if TLI is suitable for a particular case.

As there is no consistency with regard to which positive and negative outcomes or RT technical aspects are reported, the effectiveness of using retrospective analysis into the suitability of TLI is reduced. This highlights the need for further research, ideally through randomised clinical trials rather than single institution studies with small sample sizes or case studies. Randomised trials would offer several challenges due to the limited use of this technique. However, if all relevant health professionals, such as transplant physicians, were educated about the potential benefit of TLI, then it may be possible to design a multicentre trial.

It is recommended that reported outcomes for future studies included rejection episodes before and after the use of TLI, change in organ function after TLI (FEV, cardiac or renal output), medical complication(s) and death. As it is likely that this information was gathered in the previous studies and is stored in patients' notes, it might be possible to retrospectively collect this data. This would allow for a more in-depth analysis to be undertaken.

Conclusion

The use of TLI for organ rejection is uncommon compared to other non-malignant uses of RT. However, analysis of the reviewed literature indicates that TLI may be an effective means of combating cardiac and pulmonary rejection for patients that are not responding to immunosuppressive drugs.[13,14,18] Whilst it is not possible to make any firm conclusions on the role of TLI in organ rejection from the limited literature available, TLI has been shown to have the potential to decrease rejection episodes in the short term. However, the reported long-term effects in several articles suggest that TLI should be used with caution. Currently TLI is best suited to patients that are not tolerating immunosuppressive drug therapy or who are no longer responding to primary anti-rejection therapies.[13,16] TLI is not suitable as a prophylactic treatment and should only be viewed as a secondary therapy. While TLI cannot and should not replace immunosuppressive drugs such as CyA, the use of RT in organ rejection demonstrates that it has another use outside cancer treatment in addition to the other more common non-malignant conditions mentioned earlier.

RT has a role to play in organ rejection. Education of the public and other health care professionals is a key element to ensure RT is not being overlooked. Ideally future research would include randomised trials, but in an area where research is based on such small patient numbers this may not be feasible. As such, further longitudinal studies and case studies are required to ensure that practice is evidence based.

Future research should focus on defining the criteria used to describe a positive outcome, the criteria used for exclusion from studies (particular attention to RT completion) and patient demographics. This research should be multidisciplinary involving radiation therapists, immunologists, cardiothoracic surgeons and radiation oncologists. Ideally, randomised studies such as the one performed by Keogh et al.[19] in 2001, as well as longitudinal studies to confirm the work published by Tallaj et al.[13] are needed.

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Conflict of Interest

The authors declare no conflict of interest.

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