



Inguinal and Ilio-inguinal Lymphadenectomy in Management of Palpable Melanoma Lymph Node Metastasis: A Long-Term Prospective Evaluation of Morbidity and Quality of Life

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ABSTRACT

Purpose. Prospective data are lacking on long-term morbidity of inguinal lymphadenectomy including the influence of extent of surgery, use of radiotherapy, and patient factors. The aim of this study is to evaluate the effects of these factors on patient outcome, quality of life (QOL), regional symptoms, and limb volumes after inguinal or ilio-inguinal lymphadenectomy for melanoma.

Methods. Analysis of the subgroup of patients with inguinal lymph node field relapse of melanoma, treated by inguinal or ilio-inguinal lymphadenectomy in the ANZMTG/TROG randomized trial of adjuvant radiotherapy versus observation.

Results. Sixty-nine patients, 46 having undergone inguinal and 23 ilio-inguinal lymphadenectomy, with median follow-up of 73 months were analyzed. Mean limb volume

increased rapidly after surgery (7% by 3 months) and continued to increase for at least another 18 months. Patients with body mass index (BMI) ≥ 25 kg/m² had greater limb volume increase than normal-weight patients (13.3% versus 6.9%, $P = 0.030$). QOL improved over the first 18 months, but despite initial improvement, regional symptoms persisted long term. Type of surgery (inguinal or ilio-inguinal lymphadenectomy) had no demonstrably significant effect on limb volume (9.9% versus 13.4%, $P = 0.35$), QOL ($P = 0.68$), or regional symptoms ($P = 0.65$). There was no difference in overall survival between inguinal and ilio-inguinal lymphadenectomy [hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.40–1.40, $P = 0.43$].

Conclusions. Inguinal lymphadenectomy for melanoma is a potentially morbid procedure with significant increases in limb volume. Patients report reasonable QOL but may have ongoing regional symptoms. Overweight/obesity is associated with poorer QOL, increased limb volume, and regional symptoms.

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The commonest site of first relapse of cutaneous melanoma is the regional lymph nodes. In the absence of disease elsewhere, radical lymphadenectomy can result in long-term survival in up to 50% of patients.¹ For patients with inguinal lymph node field relapse, inguinal

lymphadenectomy is indicated. This procedure is associated with frequent and significant postoperative complications and long-term morbidity, with reduction in quality of life (QOL).²⁻⁵ For patients and clinicians alike, the greatest concern is the development of postoperative lymphedema.

The extent of lymphadenectomy, viz. inguinal or ilio-inguinal, and the use of adjuvant radiotherapy remain controversial issues in management of patients with groin metastatic melanoma. Up to 50% of patients undergoing ilio-inguinal lymphadenectomy will have occult iliac lymph node involvement although no clear survival benefit has been demonstrated for the more extensive procedure.⁶ Similarly, adjuvant radiotherapy is associated with a 50% reduction in the risk of lymph node field relapse but without any impact on overall survival.⁷ In managing these patients, the morbidity of more extensive surgery and/or radiotherapy is a major consideration.⁸

The aim of this study is to use data from a multicenter randomized trial to evaluate the long-term effects of lymphadenectomy for groin relapse of melanoma. Specifically, the study objectives are to examine the long-term morbidity of the procedure with specific reference to QOL, surgical morbidity, regional symptoms, and limb volume, including lymphedema, and the role of other factors including body mass index (BMI) and extent of surgery. The data from this analysis may assist decision-making in management of melanoma patients with inguinal lymph node field involvement.

METHODS

The data for this study were obtained from the recently reported Australia and New Zealand Melanoma Trials Group (ANZMTG) and Trans-Tasman Radiation Oncology Group (TROG) randomized trial (ANZMTG 01.02/TROG 02.01) of radiotherapy versus observation after lymphadenectomy for patients with melanoma lymph node field relapse (ClinicalTrials.gov no. NCT00287196). The trial, an international multicenter phase 3 study, randomized patients who had inguinal, cervical, or axillary lymphadenopathy with an estimated risk for further lymph node field relapse after lymphadenectomy of at least 25%, to either adjuvant lymph node field radiation or observation.^{7,9} Of the 217 eligible patients in the trial, 69 presented with inguinal lymphadenopathy and form the study population for this report.

Patient eligibility included inguinal node involvement of at least three nodes and/or a minimum involved lymph node size of 40 mm and/or extranodal extension of tumor; no previous history of local, regional, or distant recurrence or current evidence of other recurrence; and at least five

inguinal nodes resected and three pelvic nodes resected if an ilio-inguinal lymphadenectomy was performed. All patients had preoperative computed tomography (CT) or positron emission tomography (PET)/CT scans. Patients with known or suspected iliac or obturator lymph node involvement on preoperative imaging were not eligible. Only patients who had undergone standard radical lymphadenectomy were eligible for this study, and this was confirmed by review of the operative and pathology reports. The choice of operative procedure, viz. superficial inguinal lymphadenectomy or ilio-inguinal lymphadenectomy, was at the discretion of the treating surgeon as was routine postoperative care. After randomization, patients were reviewed 3-monthly for the first 2 years, then every 6 months to 5 years, and annually thereafter. At each visit, patients were assessed for standard surgical and radiotherapy adverse events (Common Terminology Criteria for Adverse Events version 2 and RTOG/EORTC Late Radiation Morbidity Scoring Scheme), they filled out a QOL questionnaire and an inventory of regional symptoms (Regional Symptoms Questionnaire, RSQ), and limb volume was measured.^{10,11} QOL was assessed using the Functional Assessment of Cancer Therapy-General (FACT-G) instrument, made up of four domains (physical, social, functional, and emotional well-being) and a global summary score.¹² Higher scores indicate better QOL. The RSQ assessed eight symptoms including ulceration, use of dressings, swelling and tenderness, pain on movement, range of movement, numbness, stiffness, and effect on daily living summarized by a global score. Each symptom was scored 0–4 with a global summary score of 0–32. Higher scores indicate more symptoms. Limb volume was calculated by measuring limb circumference at 10-cm intervals up the limb (to 70 cm) and summing the calculated volumes of truncated cones. Limb volume is presented as a ratio of ipsilateral to contralateral limb, expressed as a percentage. Increased volumes were classified as grade 1, minimal (<5%), grade 2, mild (≥ 5 –10%), and grade 3, moderate (≥ 10 %). Limb volume, FACT-G, and RSQ scores are shown to time of first distant relapse or end of study. The full protocol is available at https://www.anzmtg.org/documents/Intergroup_melanoma_trial_protocol_version_240407.pdf. This study was approved by the Human Research Ethics Committee of the Peter MacCallum Cancer Center.

Details of the statistical methods employed were presented previously.⁷ In summary, frequency data were analyzed using conditional exact tests and continuous data with *t*-tests. All times are measured from date of randomization. Standard Kaplan–Meier survival curves were created and compared with the log-rank test. Limb volume analyses are presented as a mean limb volume ratio compared at each time point (*t* test) and globally with respect to

an area-under-the-curve (AUC) statistic; this latter analysis was based on the volume ratio means and their estimated covariance matrix. Groups were also compared with respect to maximum grade of lymphedema. Analyses of QOL and the RSQ included comparison of mean (and mean change-from-baseline) QOL and RSQ at individual time points using *t*-tests, and a global comparison of curves over the time interval considered using an AUC statistic. One patient randomized to ART did not receive radiotherapy; for the purposes of this study, patients were analyzed according to treatment received. All *P* values are two-sided. No formal adjustment for multiple comparisons was made. Analyses were carried out using the R statistical package.¹³

RESULTS

Of the 69 eligible patients with inguinal lymphadenopathy who were randomized in the ANZMTG/TROG trial, 34 received adjuvant radiotherapy and 35 underwent observation only. Median potential follow-up time was 73 months. Inguinal lymphadenectomy was performed in 46 patients and ilio-inguinal lymphadenectomy in 23 patients (Table 1). Similar proportions of patients in the two surgical groups received adjuvant radiotherapy. The median age of the patients was 55 years, and approximately two-thirds were male (Table 1). Among the 23 patients who underwent ilio-inguinal lymphadenectomy, 11 (48%) had iliac or obturator lymph nodes containing tumor in addition to involved inguinal lymph nodes. The only difference between the two surgical groups was a slightly higher number of involved lymph nodes in patients receiving ilio-inguinal lymphadenectomy (Table 1). The type of surgical procedure was related to the treating institution ($P = 0.004$, 8 *df*).

The median body mass index (BMI) was 26.8 kg/m² (recorded in 63 patients), and overall 16 patients (25%) were overweight (BMI ≥ 25 –29.9 kg/m²) and 22 (35%) were obese (BMI ≥ 30 kg/m²). The distribution of BMI ≥ 25 kg/m² was similar when comparing patients by the main study intervention (adjuvant radiotherapy or observation) ($P = 0.24$) or surgical procedure ($P = 0.49$).

Mean limb volume ratio (ipsilateral to contralateral) and its 95% confidence interval (CI) at each time point by surgical procedure and BMI are shown in Fig. 1. The first limb volume measurement was made at time of randomization (within 12 weeks of the lymphadenectomy), prior to commencement of radiation, where this occurred. By that time, the average increase in the volume of the treated limb compared with the contralateral limb was 7.0%. No differences in this first volume measurement were found when comparing patients by major study intervention

(radiotherapy or observation) or type of surgery (7.0% and 7.3%, $P = 0.91$ for inguinal and ilio-inguinal lymphadenectomy, respectively), but patients with BMI ≥ 25 kg/m² already had a significant increase in limb volume compared with patients with BMI < 25 kg/m² (9.5% and 4.3%, respectively; $P < 0.046$) (Fig. 1).

For patients who did not receive radiotherapy or with BMI < 25 kg/m², mean limb volume increased over the first 18 months then remained stable over the remainder of the study. Patients with BMI ≥ 25 kg/m² had a mean limb volume increase of 13.3% over the duration of the study compared with a limb volume increase of 6.9% in patients with BMI < 25 kg/m² (mean difference 6.4%, $P = 0.030$). The increase in limb volume in patients with BMI < 25 kg/m² remained relatively stable after 18 months for the remainder of the study. Type of surgery was not associated with a significant difference in long-term limb volume (mean volume ratio over the study, inguinal and ilio-inguinal lymphadenectomy 9.9% and 13.4%, respectively, mean difference 3.5%, $P = 0.35$), nor was there a difference when grade of lymphedema was compared ($P = 0.92$). Among patients with BMI ≥ 25 kg/m², limb volume was greater in patients undergoing ilio-inguinal compared with inguinal lymphadenectomy (mean difference 11.6%, $P = 0.048$). For patients with BMI < 25 kg/m², there was no significant difference in limb volume between the two surgical procedures (mean difference 4.5%, $P = 0.11$).

Long-term surgical adverse events (grade 2–4) were seen in 39 (62%) of 63 patients (Table 2). There were no treatment-related deaths. There were two grade 4 toxicities (cellulitis requiring inpatient care and wound breakdown requiring inpatient care). In addition, 10 patients had long-term grade 3 surgical toxicity, 27 grade 2 toxicity, and 23 grade 1 toxicity. There was no apparent difference in the number of adverse events by type of lymphadenectomy [grade 2–4, inguinal 28 of 41 (68%) and ilio-inguinal 11 of 22 (50%), $P = 0.15$]. However, both pain and joint (hip) discomfort were more common among patients receiving inguinal lymphadenectomy ($P = 0.083$ and $P = 0.028$, respectively; Table 2).

Long-term radiation-associated toxicities (grade 2–3) were seen in 21 (75%) of 28 patients. There were no grade 4 radiotherapy adverse events. There were no apparent differences in any of the radiation-related toxicities between the two surgical groups (Table 2).

QOL as assessed with the FACT-G instrument demonstrated no significant differences for any of the domains or global score between the two surgical groups ($P = 0.68$) (Table 3; Fig. 2). Similarly, no significant difference in the RSQ was observed between the two surgical groups ($P = 0.65$) (Table 3; Fig. 3). The FACT-G score was the lowest (indicating poorer QOL) at the time of

TABLE 1 Patient and tumor details for all patients by type of operation

	Inguinal lymphadenectomy	Ilio-inguinal lymphadenectomy	All patients	<i>P</i>
All patients	46	23	69	
Median (IQR) age (years)	55.5 (44–69)	54.0 (45.5–68.5)	55.0 (45–69)	0.74
Sex				
Male	30 (65%)	15 (65%)	46 (65%)	1.00
Female	16 (35%)	8 (35%)	23 (35%)	
Lymph nodes, median (range)				
No. of positive nodes	3 (2–4)	4 (2–5)	3 (2–4)	0.091
No. of nodes removed median (range)	10 (8–14)	18 (14–22.5)	13 (10–17)	< 0.001
Median (IQR) maximum tumor size (mm)	35 (20–50)	40 (26–50)	40 (24–50)	0.40
Extranodal extension				
Nil/< 2 mm	38 (83%)	18 (78%)	56 (81%)	0.67
≥ 2 mm	8 (17%)	5 (22%)	13 (19%)	
Treatment received				
Adjuvant radiotherapy	21 (46%)	13 (57%)	34 (49%)	0.40
Observation	25 (54%)	10 (43%)	35 (51%)	
Body mass index (kg/m ²)				
Median (IQR)	27.3 (23.3–32.0)	26.4 (22.4–28.9)	26.8 (22.8–31.6)	0.30
< 25	15 (37%)	10 (45%)	25 (40%)	0.49
≥ 25	26 (63%)	12 (55%)	16 (25%)	
Unknown	5 (11%)	1 (4%)	6 (9%)	
ECOG status				
0	29 (63%)	15 (65%)	44 (64%)	0.86
1	17 (37%)	8 (35%)	25 (36%)	

Percentages are column percents

P is the *P* value for testing the hypothesis that the row variable is distributed the same for each operation type

One patient randomized to radiotherapy did not receive it

IQR interquartile range, *ECOG* Eastern Cooperative Oncology Group

randomization, shortly after lymphadenectomy, improved over the next 12–18 months, then remained relatively stable for the remainder of the study. Similarly, the RSQ score at randomization was also as high (indicating a greater burden of regional symptoms) as at any time during the period of follow-up and dramatically improved over the first 12–18 months then remained relatively stable thereafter (Fig. 3). The FACT-G score plateaued at a level consistent with reasonable QOL, but the RSQ score plateaued at a level consistent with ongoing symptoms. Patients with BMI ≥ 25 kg/m² experienced worse QOL (global FACT-G mean difference 8.6, *P* = 0.001) and more regional symptoms (RSQ mean difference 4.3, *P* = 0.002) (Figs. 2, 3). Both QOL and RSQ for patients with BMI ≥ 25 kg/m² improved over the 24 months from randomization and remained relatively stable thereafter (Figs. 2, 3).

Ilio-inguinal lymphadenectomy was associated with longer relapse-free survival (RFS) compared with inguinal lymphadenectomy (HR 0.50, 95% CI 0.29–0.87, *P* = 0.024) (Fig. 4). A test for the proportional hazards model showed significant deviation from this assumption (*P* = 0.002). It appears that the relapse rate in the first 6 months was worse for ilio-inguinal lymphadenectomy (10/23 relapses) compared with inguinal lymphadenectomy (13/46) but significantly lower thereafter (3 and 29 relapses, respectively). All deaths followed a relapse. No statistically significant difference in overall survival between lymphadenectomy types was observed (HR 0.75, 95% CI 0.40–1.40, *P* = 0.43), although, again, there was a significant departure from the proportional hazards assumption (*P* = 0.013). The 5-year overall survival rate for all patients was 38% (95% CI 27–50%).

On univariable analyses (see Supplementary Data), longer RFS was related to absence of significant (> 2 mm) extranodal extension (HR 0.43, 95% CI 0.18–1.01,

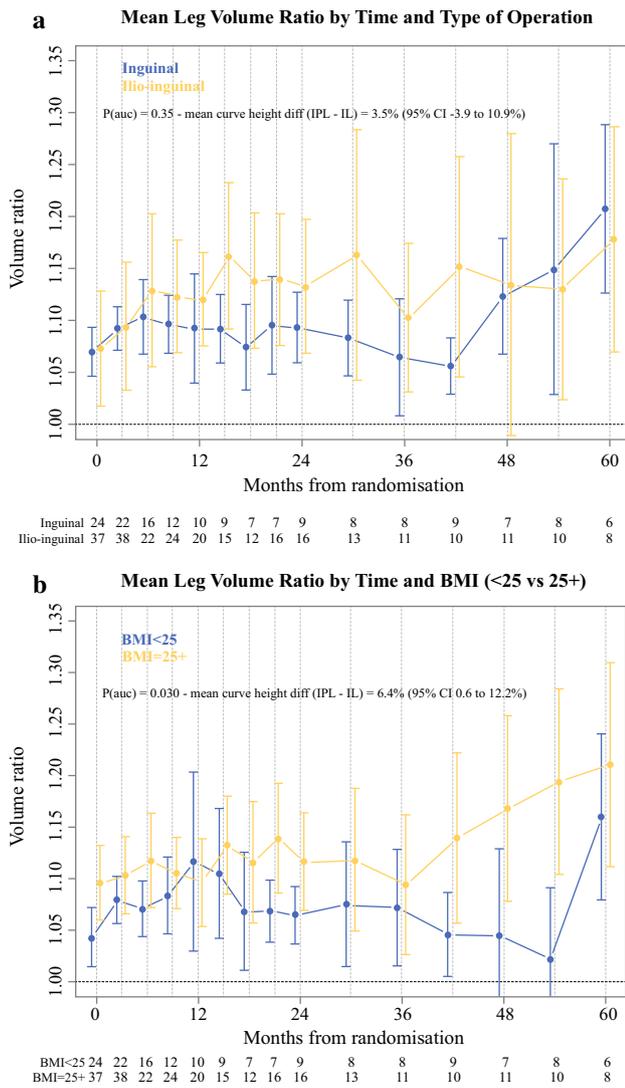


FIG. 1 Mean of limb volume ratio at standard time points by: **a** type of operation, inguinal and ilio-inguinal lymphadenectomy, and **b** normal weight (BMI < 25 kg/m²) and overweight/obese (BMI ≥ 25 kg/m²). Bars represent standard error of the mean

P = 0.013) and ilio-inguinal lymphadenectomy (HR 0.50, 95% CI 0.29–0.87, *P* = 0.024) but not treatment arm (radiotherapy or observation), sex, number of lymph nodes involved, or BMI (Fig. 4). Shorter overall survival was significantly related to presence of extensive extranodal extension (HR 3.1, 95% CI 1.2–8.1, *P* = 0.001) but not type of operation (HR 0.75, 95% CI 0.40–1.40, *P* = 0.43), treatment arm (adjuvant radiotherapy or observation), sex, number of lymph nodes involved, or BMI.

Time to first relapse in a lymph node field was not related to any major variables; inguinal lymphadenectomy patients had a higher lymph node field relapse rate than ilio-inguinal patients, although this was not statistically significant (ilio-inguinal:inguinal lymphadenectomy,

HR 0.46, 95% CI 0.18–1.15, *P* = 0.16). It was not possible to determine the exact nature of regional relapse due to the complexity of recurrence patterns.

DISCUSSION

The risk of morbidity after inguinal and ilio-inguinal lymphadenectomy is substantial. Contemporary reports focus on immediate postoperative complications, or short-term complications which occur in up to 70% of cases and include wound infection and dehiscence, skin edge necrosis, seroma formation, and early lymphedema.^{2–4,14,15} Two recent surveys of the literature report considerable variation in the frequency of these complications, likely due to the retrospective nature of most of the studies, variations in definitions of the complications, and heterogenous patient populations.^{2,5} The present study, which included only patients with American Joint Committee on Cancer (AJCC) 7th edition stage IIIB and C melanoma, collected standard morbidity data prospectively at multiple time points and demonstrated that long-term surgical complications of inguinal and ilio-inguinal lymphadenectomy are common (grade 2+ , 62%) but were mostly minor or moderate (grade 2 43%; grade 3 16%, grade 4 3%). Extent of surgery had little impact on long-term toxicity apart from increased joint (hip) discomfort in inguinal lymphadenectomy patients. As described previously in this patient group, only tissue fibrosis and long-term pain were more commonly seen in patients receiving radiotherapy, but overall grade 2–4 toxicity was the same in the radiotherapy and observation groups.⁷ Elevated BMI (≥ 25 kg/m²) has frequently been associated with higher risk of acute wound complications, particularly infection and wound edge necrosis.^{2,3,15,16} In contrast, the current study found that, although long-term surgical or radiation-related adverse events were common (60%), most were minor (grades 1 and 2) and obesity/overweight was not related to development of long-term standard toxicities apart from lymphedema (*P* = 0.031) (Table 2; Fig. 1). It is important to note that patients in the current study, in contrast to many prior publications which included completion lymphadenectomy for sentinel node detected metastases, all underwent surgery for palpable groin lymphadenopathy (median lymph node size 40 mm, median three positive nodes, 50% with extranodal extension) with no clinical or radiological evidence of disease in the pelvis.

There are many reports documenting lymphedema following inguinal or ilio-inguinal lymphadenectomy, but the overwhelming majority are retrospective studies measuring lymphedema at variable time points and using a variety of assessment techniques and not uncommonly patient- or clinician-reported subjective evaluations. In a large survey,

TABLE 2 Standard late surgical and radiotherapy adverse events, grade 2 or worse by operation type (inguinal or ilio-inguinal lymphadenectomy)

	Inguinal lymphadenectomy	Ilio-inguinal lymphadenectomy	All patients	<i>P</i>
Surgical toxicity				
All patients	41	22	63	
Subcutaneous tissue fibrosis	20/40 (50%)	9/22 (57%)	29/62 (33%)	0.50
Pain	14/41 (34%)	3/22 (13%)	17/63 (25%)	0.083
Nerve damage	8/41 (20%)	6/22 (26%)	14/63 (20%)	0.48
Joint	8/41 (27%)	0/22 (0%)	8/63 (12%)	0.028
Other	11/41 (27%)	7/22 (29%)	18/63 (29%)	0.68
Combined	28/41 (68%)	11/22 (50%)	39/63 (62%)	0.15
Radiation toxicity				
All patients	19	9	28	
Skin	8/19 (42%)	6/9 (67%)	14/28 (50%)	0.23
Pain	7/19 (37%)	1/9 (11%)	8/28 (64%)	0.17
Soft tissue	12/19 (63%)	7/9 (78%)	19/28 (68%)	0.45
Bone	1/19 (5%)	0/9 (0%)	1/28 (4%)	0.49
Joint	4/19 (21%)	0/9 (0%)	4/28 (14%)	0.14
Nerve	3/19 (16%)	3/9 (33%)	6/28 (21%)	0.30
Other	5/19 (26%)	5/9 (56%)	10/28 (36%)	0.21
Combined	13/19 (68%)	8/9 (89%)	21/28 (75%)	0.24

Cell entries are number (percentage) of grade 2 or worse adverse events

There were two G4 surgical AEs: one subcutaneous tissue and one other, both in inguinal lymphadenectomy patients (cellulitis requiring inpatient care and wound breakdown requiring inpatient care)

There were no G4 radiotherapy adverse events

the pooled estimate of lymphedema incidence was 28% (95% CI 17–42%), but the incidence as detected by objective means, e.g., water displacement or limb circumference measurements, was twice that of subjective assessment.¹⁷ Furthermore, prospective studies using objective measurements of limb volume increase of at least 5% found an even higher incidence of lymphedema of 45% at 3 months and 64% at 12 months.^{2,18} In the current study, in which limb volume was measured prospectively over a protracted period, the incidence of lymphedema as defined by limb volume increase of at least 5% compared with the contralateral limb was even higher, at 72%. The initial lower limb volume measurement in the study was performed within 12 weeks of inguinal lymphadenectomy, by which time the average increase in limb volume compared with the contralateral limb was 7%, indicating rapid establishment of mild limb swelling. For patients who were not overweight/obese or did not undergo radiotherapy, there was little change in limb volume beyond 18 months after randomization. In contrast, patients who received adjuvant radiotherapy had a greater increase in limb volume by 12 months, and this increase continued to increase for at least 2 years after randomization then remained relatively stable over the remainder of the study. The type

of operation did not appear to have any differential effect on limb volume, although further interrogation of the data indicated that the more extensive procedure of ilio-inguinal lymphadenectomy caused a greater increase in limb volume among patients who were overweight/obese. A recently published survey of reports examining the extent of surgery found a pooled incidence of lymphedema of 42% in patients undergoing ilio-inguinal lymphadenectomy compared with 18% in patients undergoing inguinal lymphadenectomy, although the authors point out that the quality of the reviewed studies varied greatly.² The current report and others have failed to confirm a major increase in limb volume for ilio-inguinal compared with inguinal lymphadenectomy.^{6,19–21} A possible explanation, observed in the present study, is the effect that overweight/obesity may play a role in the development of lymphedema in patients with the added liability of more extensive surgery (i.e., ilio-inguinal lymphadenectomy) or radiotherapy.

The reduced QOL scores recorded immediately after lymphadenectomy at the time of randomization improved over the first 12–24 months, highlighting the significant impact of lymphadenectomy on QOL. The FACT-G scores after 12 months indicate that QOL was acceptable to patients despite quite significant regional symptoms as

TABLE 3 Quality of life measures by type of operation

	Inguinal lymphadenectomy mean	Ilio-inguinal lymphadenectomy mean	Difference (inguinal – ilio-inguinal) (95% CI)	<i>P</i> value
FACT-G (<i>n</i>)	39	18		
FACT-G	89.2	90.8	– 1.6 (– 6.1 to 9.3)	0.68
Physical	23.8	24.4	– 0.6 (– 2.6 to 1.5)	0.59
Social	24.0	24.7	– 0.7 (– 2.4 to 1.0)	0.43
Functional	22.0	22.2	– 0.2 (– 3.4 to 2.9)	0.88
Emotional	19.4	19.4	0.0 (– 2.7 to 2.7)	0.99
RSQ (<i>n</i>)	39	18		
RSQ	9.6	8.6	1.0 (– 3.3 to 5.3)	0.65
Lymphedema (<i>n</i>)	46	23		
% relative increase	9.9%	13.4%	– 3.5% (– 10.9 to 3.9%)	0.35
Grade of Lymphedema (<i>n</i>)	46	23		
Grade 0/1 (≤ 5%)	12 (26%)	7 (30%)	– 4%	0.14 (overall, 2df)
Grade 2 (> 5–10%)	28 (61%)	9 (39%)	22%	0.45 (trend, 1df)
Grade 3 (> 10%)	6 (13%)	7 (30%)	– 17%	

Functional Assessment of Cancer Therapy–General (FACT-G) including global combined score and individual domains: higher score indicates better QOL

FACT-G values are “mean QOL values over 60 months” (AUC from 0 to 60 months divided by 60)

Regional Symptoms Questionnaire (RSQ) combined score of eight domains; higher score indicates more symptoms

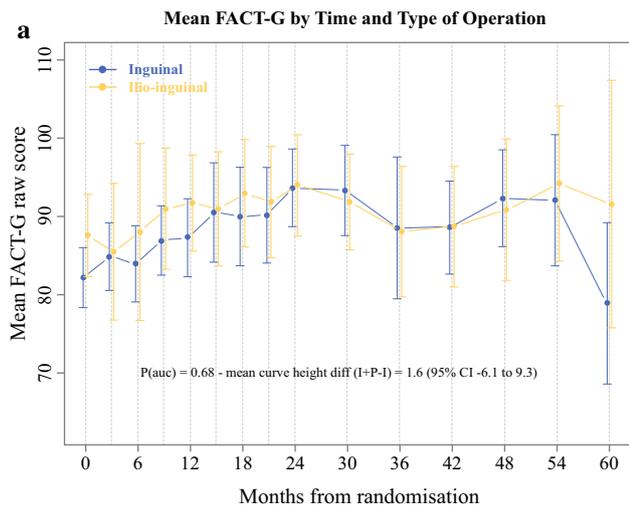
RSQ values are raw scores expressed as a percentage of the maximum score

Scores given as mean area under the curve of assessments over the course of the study

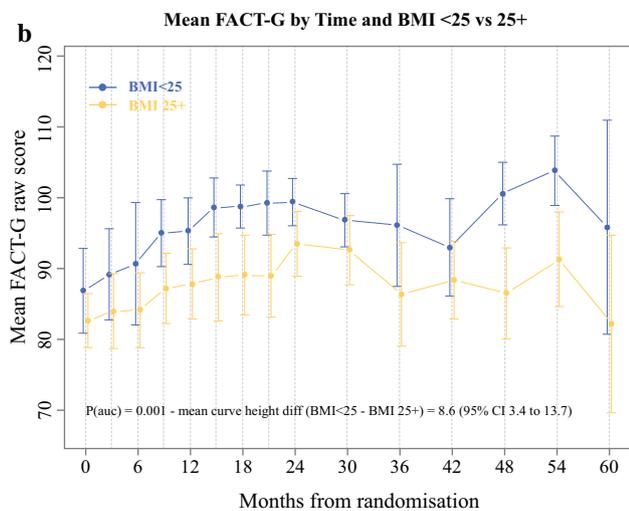
reported by the RSQ. Possible explanations include an acceptance by the patient of limitations and a desire to move on with their lives, an observation which has been noted previously.^{20,22} Alternatively, the QOL tool was not sensitive to modest differences, although the FACT-G QOL tool has been validated as an accurate and reproducible instrument for assessing QOL.¹² Symptoms such as discomfort, heaviness, and fatigue are common after lymphadenectomy and are not necessarily correlated directly with the extent of increase in limb volume. What has not been well appreciated is the strong relationship between these symptoms and limb swelling of even modest degree and how they are impacted by patient anxiety levels and coping skills.^{22,23} The assessment of patient experience after lymphadenectomy is likely more complicated than reporting of symptoms or measurement of limb volume and probably reflects a complex relationship with patient factors.^{18,24–26}

Although this study indicates that addition of ilio-inguinal lymphadenectomy imparts little extra morbidity for most patients with palpable lymphadenopathy, the important question of whether it improves survival remains controversial.²⁷ The improved RFS in patients undergoing ilio-inguinal lymphadenectomy as noted in this study must be interpreted with caution as the surgical intervention was not randomized and this study was neither planned nor powered to evaluate this question. However, as the more extensive surgery identified additional tumor-bearing lymph nodes in nearly 50% of cases, the issue of the extent of the lymphadenectomy justifies further evaluation with a randomized trial such as the EAGLE-FM study (<https://clinicaltrials.gov/ct2/show/NCT02166788>).

This study was a post hoc analysis of a subgroup of patients, with the obvious limitations. The use of radiotherapy was randomized, but not the type of surgical procedure. Limitations of this study also include the relatively small patient numbers, particularly within some



Inguinal	39	37	34	28	22	17	13	17	17	13	11	10	7	6	3
Ilio-inguinal	18	16	8	10	12	9	9	10	10	9	7	8	8	6	4

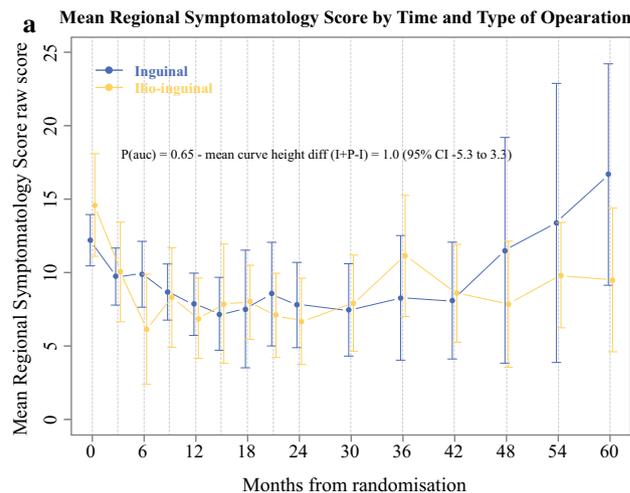


BMI<25	19	18	14	10	10	7	7	7	8	7	6	5	6	3	3
BMI 25+	38	30	23	24	21	17	14	18	17	14	11	12	8	8	3

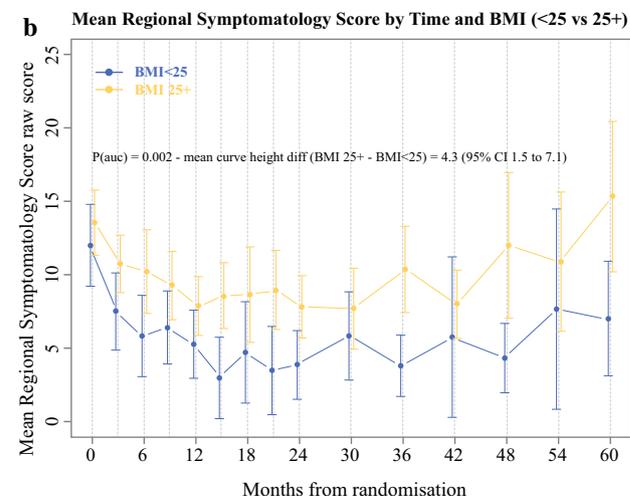
FIG. 2 Mean FACT-G score at standard time points by **a** operation, inguinal and ilio-inguinal lymphadenectomy, and **b** normal weight (BMI < 25 kg/m²) and overweight/obese (BMI ≥ 25 kg/m²). Bars represent standard error of the mean

subgroups. However, standard data were collected prospectively at regular intervals for an extended period of time and provide the most comprehensive evaluation of patient experience after inguinal and ilio-inguinal lymphadenectomy to date, to the best of the authors' knowledge.

In summary, this study confirms that the onset of lymphedema after inguinal or ilio-inguinal lymphadenectomy is rapid (within 3 months). For patients of normal weight who do not receive radiotherapy, mean limb volume continues to increase over the first 18 months then remains relatively stable thereafter. Obesity/overweight (BMI ≥ 25 kg/m²) is associated with greater limb volume



Inguinal	34	36	33	26	21	16	13	15	16	13	11	10	6	5	3
Ilio-inguinal	17	15	7	10	8	9	10	10	9	9	6	7	7	6	4



BMI<25	15	18	12	10	8	6	7	6	8	7	5	4	6	3	3
BMI 25+	31	28	23	22	20	16	14	17	16	14	11	12	6	7	3

FIG. 3 Mean Regional Symptoms Score (RSQ) at standard time points by **a** operation, inguinal and ilio-inguinal lymphadenectomy, and **b** normal weight (BMI < 25 kg/m²) and overweight/obese (BMI ≥ 25 kg/m²). Bars represent standard error of the mean

increases, poorer QOL, and worse regional symptoms than occur in patients with normal BMI; these changes develop early and rapidly after surgery and continue to worsen for at least 24 months. From our previous report, adjuvant radiotherapy was identified as causing significant increases in limb volume (15.5% vs. 7.7%, *P* = 0.014) and increased regional symptoms compared with patients not receiving radiotherapy. The increased limb volume and worse regional symptoms plateau approximately 18 months after radiotherapy and remain relatively stable thereafter.⁷ The more extensive procedure of ilio-inguinal lymphadenectomy is only associated with an increase in limb volume for patients receiving radiotherapy or who are overweight/obese.

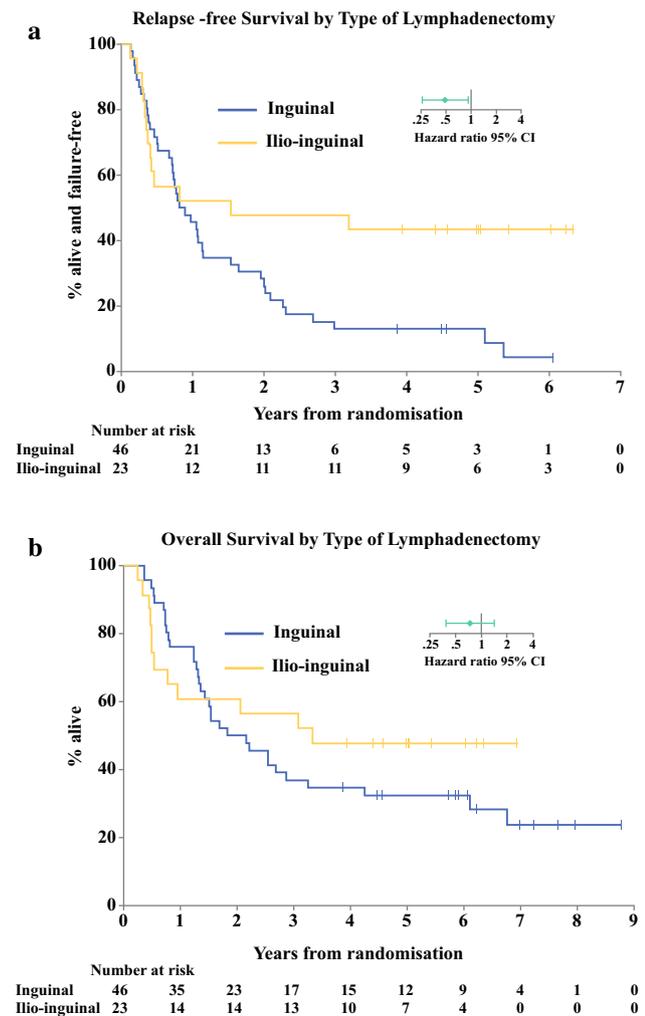


FIG. 4 a Relapse-free and **b** overall survival by type of surgical procedure, inguinal and ilio-inguinal lymphadenectomy

Inguinal or ilio-inguinal lymphadenectomy causes significant regional symptoms and deterioration in QOL in the immediate postoperative phase, but over the long term, patients report acceptable QOL but with a significant incidence of ongoing regional symptoms.

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