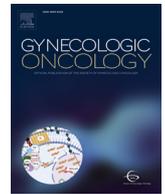




Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Challenges in lower limb lymphoedema assessment based on limb volume change: Lessons learnt from the SENTIX prospective multicentre study

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HIGHLIGHTS

- A volumetric threshold for lower limb lymphoedema diagnosis should be increased to $\geq 15\%$.
- LLL diagnosis requires repeated measurements and a prolonged follow-up period > 1 year.
- Patient-reported swelling should only be used as an adjunct to objective measurement.

ARTICLE INFO

Article history:

Received 14 September 2021

Received in revised form 18 October 2021

Accepted 20 October 2021

Available online xxxx

ABSTRACT

Background. Lower limb lymphoedema (LLL) is the most disabling adverse effect of surgical staging of pelvic lymph nodes. However, the lack of standardisation of volumetric LLL assessment hinders direct comparison between the studies and makes LLL reporting unreliable. The aim of our study is to report outcomes from a prospective trial that have implications for LLL assessment standardisation.

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<https://doi.org/10.1016/j.ygyno.2021.10.089>

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Please cite this article as: M. Borčinová, V. Ragosch, J. Jarkovský, et al., Challenges in lower limb lymphoedema assessment based on limb volume change: Lessons learnt from the..., Gynecologic Oncology, <https://doi.org/10.1016/j.ygyno.2021.10.089>

Keywords:

Lower limb lymphedema
Limb volume change
Transient edema
Assessment standardisation
Cervical cancer

Methods. In the prospective international multicentre trial SENTIX, a group of 150 patients with stage IA1–IB2 cervical cancer treated by uterine surgery with bilateral sentinel lymph node biopsy was prospectively evaluated by objective LLL assessment, based on limb volume change (LVC) using circumferential limb measurements and subjective patient-reported swelling. The assessments were conducted in six-month periods over 24 months post-surgery.

Results. Patient LVC substantially fluctuated in both positive and negative directions, which were comparable in frequency up to $\pm 14\%$ change. Thirty-eight patients experienced persistent LVC increase $>10\%$ classified as LLL, with nine months median time to onset. Some 34.2% of cases experienced onset later than one year after the surgery. Thirty-three patients (22%) experienced transient oedema characterised as LVC $>10\%$, which resolved without intervention between two consequent follow-up visits. No significant correlation between LVC $>10\%$ and a patient-reported swelling was observed.

Conclusions. Given that we observed comparable fluctuations of the the lower-limb volumes after surgical treatment of cervical cancer in both positive and negative direction up to $\pm 14\%$, the diagnostic threshold for LLL diagnosis based on LVC should be increased to $>15\%$ LVC. The distinction of transient oedema from persistent LLL requires repeated measurements. Also, as one-third of LLL cases are diagnosed >1 -year post-surgery, a sufficient follow-up duration needs to be ensured. Patient-reported swelling correlated poorly with LVC and should only be used as an adjunct to objective LLL assessment.

Trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02494063): NCT02494063

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1. Introduction

Lower limb lymphoedema (LLL) is the most disabling adverse effect of surgical staging of pelvic lymph nodes [1]. It is caused by disruption or obstruction of central lymphatic trunks and leads to accumulation of protein-rich interstitial fluid in tissue spaces resulting from a lack of proper centripetal drainage [2]. This morbidity can limit patients' mobility and have a substantial impact on quality of life [3,4].

The incidence of LLL in patients after surgical treatment of cervical cancer is reported in a wide range of 0–62% [5–7]. The main reason for such a wide variation in LLL observation is the lack of assessment standards, including the use of different classification systems and, most importantly, the method of the assessment [8]. The majority of published studies are based either on retrospective data [6,7], do not define the assessment methods [9,10], are based solely on subjective patient-reported changes in the limbs [11,12], or they use physical examination without objective measurement [3]. Even when an objective method is used, such as lymphoscintigraphy, magnetic resonance imaging, or volumetric measurements, neither a threshold for LLL diagnosis nor a correlation between the methods has been established [4,13]. The length of post-treatment follow-up of published studies also varies, regularly equaling one year or less, and the final outcomes are frequently based on single endpoint assessment [14–16]. For those reasons, direct comparisons between previously reported LLL incidences are hindered, always requiring the reported results to be put in context with the respective methodology and classification used.

Even though substantial research is available regarding upper limb lymphedema following treatment of breast cancer [17], the comparison with LLL development after cervical cancer treatment is not straightforward. Since axillary lymph node removal is typically ipsilateral, breast cancer-related lymphedema affect only one upper extremity [18]. On the contrary, surgical LN staging is always bilateral in the pelvis [19,20], therefore the comparison between affected/ unaffected limbs does not represent viable option for LLL screening.

The SENTIX trial is an ongoing prospective international observational study with the main endpoint being the oncological outcome of cervical cancer patients treated by uterine surgery with sentinel lymph node biopsy without systematic pelvic lymphadenectomy (PLND). Incidence of LLL is the pre-planned secondary endpoint of the study, prospectively analysed using serial circumferential measurements in anatomically standardised levels performed in six-month intervals over the course of 24 months post-surgery. The main results of the interim analysis concerned with LLL incidence were recently published [21]. The aim of this study is to present outcomes related to LLL

assessment and the correlation between subjective and objective evaluations, which we find important for the standardisation of LLL assessment in future studies.

2. Materials and methods

2.1. Study design and participants

In this pre-planned analysis, data were analysed from 150 patients who were enrolled between 05/2016 and 11/2017 and treated per protocol in the SENTIX trial with two years' follow-up data availability. SENTIX (SENTinel lymph node in cervIX cancer) is a prospective, multi-centre, observational trial on SLN biopsy in patients with early-stage cervical cancer with the primary endpoint being recurrence rate at the 24th month of follow-up. The pre-planned secondary endpoint was the assessment of LLL incidence.

Details of inclusion and exclusion criteria were published elsewhere [20–22]; in short: cervical cancer patients with FIGO 2009 [23] stage IA1 with lymphovascular space invasion, IA2, or IB1, who lacked suspicious lymph nodes on preoperative imaging, had a common histological tumour type, and the largest tumour diameter less than 4 cm (less than 2 cm for fertility-sparing procedure) underwent surgical procedure with sentinel lymph node dissection, without PLND.

SENTIX was conducted as a European Network of Gynaecological Oncology Trial Groups (ENGOT) trial (ENGOT Cx2) and was led by the Central and Eastern European Gynaecologic Oncology Group (CEGOG; CEGOG Cx1). The study was performed according to ENGOT Model A [24]. The protocol was approved by the Institutional Review board of the leading institution (General University Hospital in Prague, Czech Republic) in 2015. Institutional review board approval of all participating sites was a prerequisite for participation. All participating patients signed informed consent before study enrolment. The study was performed in accordance with the Declaration of Helsinki.

2.2. Objective secondary LLL assessment

Objective LLL assessment was based on volumetric change calculated based on circumferential limb measurements. Each limb was measured at five standardised levels (C1–C5): C1–10 cm below anterior superior iliac spine; C2–10 cm above midpoint of the knee joint; C3–10 cm below midpoint of the knee joint; C4–10 cm above medial ankle (malleolus); C5–level of medial ankle (malleolus) (Supplementary Fig. 1). All measurements were performed under uniform conditions: (i) a flexible tape measure was used; (ii) patient was lying still

in a supine, relaxed position, with the leg straight; (iii) markings were applied on the skin in five defined levels; and (iv) the tape was kept at right angles to the limb length axis in all girth measurements.

The total limb volume was calculated as a sum of the volumes of four individual segments (eq. 1). The volume of each limb segment was calculated based on the truncated cone formula; where h = height of the segment, A = circumference at the top of the segment, B = circumference at the bottom of the segment.

$$V_{limb} = \sum \frac{(h) * (A^2 + A * B + B^2)}{12 * \pi} \quad (1)$$

Above-knee volume (thigh volume) was calculated as a volume of the segment between C1 and C2 levels. The below-knee volume (calf and ankle volume) was calculated as a sum of segments C3–C4 and C4–C5.

Limb volume change, characterised as a volume increase $\geq 10\%$ from pre-operative volume persisting over a period of at least six months (i.e., observed at least during the two consequent follow-up visits), was classified as secondary LLL [25]. Any temporary episode of swelling (LVI $> 10\%$) that was not observed during the consequent follow-up visit was considered a transient oedema triggered by causes other than LLL. Limb volume assessment was performed at the preoperative visit and subsequently during follow-up visits, every six months for 24 months post-surgery.

2.3. Patient-reported LLL

At each follow-up visit, all patients were asked about their subjective assessment of each lower leg swelling during the past six months, separately for five levels: loin, thigh, calf, ankle, and foot. For swelling above and below the knee, reporting of swelling in the loin and thigh and ankle and foot, respectively, were pooled (reported swelling in either part of pooled answers was considered a positive response).

2.4. Statistics

Standard descriptive statistics were applied in the analysis; absolute and relative frequencies for categorical variables and median supplemented by 5th–95th percentile for continuous variables. Chi-Square goodness of fit test was adopted for the computation of statistical significance of differences in expected balanced numbers of positive and negative changes. Statistical significance of relationship between objective and subjective evaluation of lymphoedema was tested using Fisher's exact test and the Pearson correlation coefficient for binary data and its statistical significance. $\alpha = 0.05$ was adopted as a level of statistical significance in all analyses. Analysis was computed using SPSS 25.0.0.1 (IBM Corporation, 2019) and R with package ggplot2.

3. Results

3.1. Patient characteristics

The median age of the patients at the time of surgery was 43 years. Out of the analysed patients, 53% were in the normal BMI range, 27% were in the range of 26–30, and 20% of patients had a BMI over 30 kg/m². The majority of patients had pre-treatment FIGO stage IB1 (128 patients/85.3%), preoperative tumour size ≤ 2 cm (107/71.3%), and squamous cell tumour histotype (102/68.0%). The median number of removed SLNs per patient was three (5th–95th percentile: 2–6.55). All patients underwent surgery with bilateral SLN biopsy without systematic pelvic lymphadenectomy. The full characteristics of the patients are in Supplementary Table 1, as published recently [21].

3.2. Limb volume change fluctuations

The patients were regularly followed in six-month periods over the course of 24 months. Comprehensive analyses of the lower limb volume change (LVC), for left and right limb separately, from the preoperative baseline assessment at each of the follow-up visits are displayed in Fig. 1.

LVC of the patients substantially fluctuated in both positive and negative directions. Firstly, we compared analogous positive and negative LVC increments using an established scale for LLL staging according to Best practices for the management of lymphoedema: no/subclinical LLL 0–9%; mild LLL 10–19%; moderate and severe LLL $> 20\%$ [25]. Positive and negative increments were comparable to ± 0 –9% LVC, were only marginally significant in the range of 10–19% LVC and became significant with LVC $> 20\%$ (Fig. 2A).

Subsequently, the LVC range of 10–19% was further split into two subgroups of 10–14% and 15–19%. No significant difference between the ratio of \pm increments was observed in the range of 10–14% LVC, while it turned out to be significant in a subgroup with LVC of ± 15 –19% (Fig. 2B).

3.3. Transient oedema

Transient oedema, i.e., limb volume increase $> 10\%$ that resolved without intervention between two consequent follow-up visits, was found in 22% of the patients (33/150). The majority of them (23, 69.7%) had transient oedema in both limbs. If transient oedema appeared on one of the limbs only, it never exceeded LVC of $> 13\%$. A larger LVC increase was observed only in patients who had transient oedema on both legs at the same time point (Fig. 3). The proportion of patients experiencing transient oedema remained stable for 24 months post-surgery (9, 15, 12, and 7 patients at 6, 12, 18, and 24 months, respectively).

The average incremental value of LVC for transient oedema was 13% and 12% on right and left limbs, respectively. Individual fluctuations of LVC in patients with transient oedema are depicted in Supplementary Fig. 2.

3.4. LLL onset after surgery

Persistent LVC increase $> 10\%$, not resolved by a consequent follow-up visit, was classified as LLL. Overall, 38 patients (cumulative incidence 27%) experienced persistent LLL of any stage. The median interval to LLL onset was nine months (95% CI: 7.0–11.0). LLL was diagnosed at six, 12, 18, and 24 months after surgery in 50%, 16%, 26%, and 8% of LLL-diagnosed patients (Fig. 4).

According to the traditionally used criteria, the cumulative incidence of mild (LVC 10–19%) and moderate (20–39%) LLL at 24 months reached 17.3% and 9.2%, respectively, with only one (0.7%) case of severe ($> 40\%$) LLL (for further details, refer to previously published study [21]). A cumulative incidence of 8.9% was attributed to the patients with persistent LLL in the range of 10–14%.

3.5. Correlation of patient-reported LLL with objective LVC

A detailed analysis of the relationship between objective LVC increase, irrespective of transient or persistent character of the oedema, and patient-reported swelling in limb subparts (above and below the knee) was performed. At either time point, the majority of patients experiencing an objective LVC increase $> 10\%$ did not subjectively report swelling in the respective part of the leg. Vice versa, the majority of patients subjectively reporting swelling did not have objective $> 10\%$ LVC (Fig. 5). No significant correlation between subjective and objective assessment was observed.

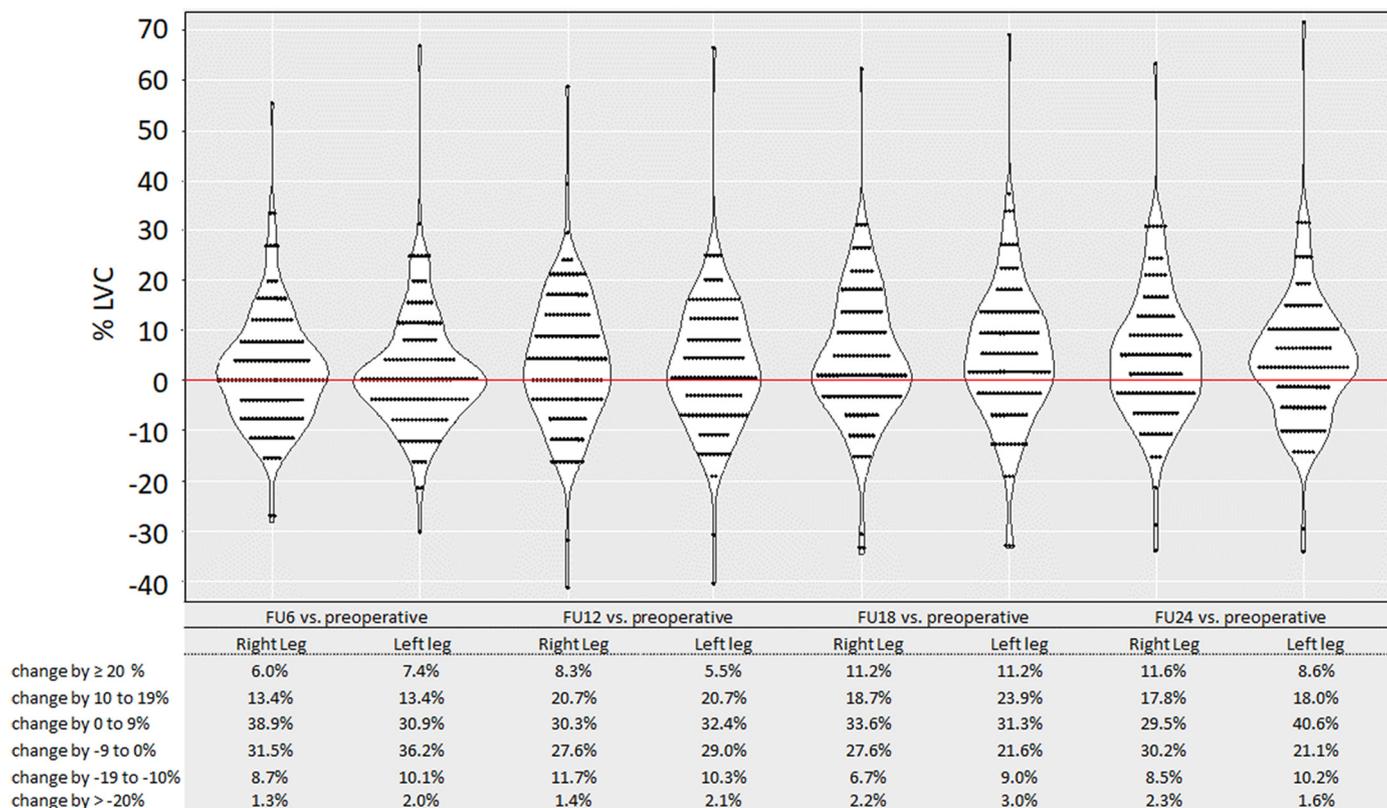


Fig. 1. Distribution of the limb volume change (LVC) of right and left lower limb during the follow-up period. Each dot on the violin plot represents the LVC of one patient's limb. 6 M: six months post-surgery; 12 M: 12 months post-surgery; 18 M: 18 months post-surgery; 24 M: 24 months post-surgery.

4. Discussion

To our knowledge, we have for the first time showed a great fluctuation of lower limb volumes after surgery in both positive and negative directions. Our results indicate that fluctuations up to 14% occur equally frequently in both positive and negative increments, suggesting that the threshold for LLL diagnosis could be set at a 15% limb volume increase.

We also reported the frequent presence of transient oedema, observed among 22% of patients, characterised as a limb volume increase of $\geq 10\%$, resolving without intervention until the subsequent follow-up measurement, highlighting a need for repeated measurements for reliable LLL assessment. Our results similarly signified the importance of prolonged follow up, as one-third of the patients (34%) developed LLL more than one year after the surgery,

Finally, a detailed analysis of the relationship between patient-reported swelling and objective LVC changes showed a poor correlation, with the majority of patients who experienced objective LVC increase not reporting any lower limb swelling.

No gold standard for measurement or defining criteria exists for LLL assessment in the clinical setting. Previously published studies reporting LLL among patients after cervical cancer treatment reported LLL incidence in the broad range of 0–62% [6,26–29]. Such a wide range is undoubtedly caused by serious variations in the methodology and LLL classification systems. The majority of the previously published studies have a retrospective design, do not report details on LLL assessment, or suffer from serious limitations in methodology (Supplementary Table 2). Since LLL assessment is only rarely routinely performed during the standard-of-care treatment, only symptomatic patients are assessed, while minimal or mild changes could be overlooked. Therefore, all studies with retrospective design likely underreport LLL incidence.

Since 2010, only 11 prospective studies reporting LLL among cervical cancer patients have been published. In two of them, the LLL assessment

method was not specified [30,31]; three of them were based solely on patient-reported assessments, using a single question inquiring about perceived limb swelling [11,12,32]; two studies utilised objective assessment methods, bioimpedance spectroscopy [33] and ultrasonography [26] but were limited by a small cohort size with 28 and 35 patients, respectively. In the remaining four publications, LLL diagnosis was based on an objective limb volume measurement [14,15,34,35]. In the first two studies, however, the follow-up period lasted only six months and did not consider transient oedema [14,35]. In the second study, a non-standard threshold of 2% difference was employed, although it was supplemented by symptoms assessment by lymphoedema specialist. The follow-up period was also limited to one year [15]. Finally, the multi-institutional LEG study (the Lymphedema and Gynecologic cancer study) prospectively evaluated incidence and risk factors for LLL development in 1054 gynaecological-cancer patients, including 138 cervical cancer patients who underwent radical surgery with systematic PLND, and reported incidence of LLL at two years after the surgery, utilising a 10% LVC increase threshold. However, in this study, any exceedance of the 10% threshold at either of the (seven) follow-up visits was considered LLL, thus disregarding transient oedema from other causes [34].

The threshold of 10% LVC increase for LLL diagnosis, utilised in the majority of volume-change based LLL studies, is based on a prior paper from Spillane et al. [36], who correlated volume thresholds with patient-reported outcomes. The threshold is a conversion of the study outcome which showed that a $> 7\%$ increase in the sum of circumferential measurements (equalling approximately 10% increase in limb volume) at six defined sites provided a robust definition of LLL with a sensitivity of 50% and specificity of 100%. The 10% threshold is also based on an international consensus document of Best practice for the management of lymphoedema [25], which, however, recommended using the 10% increase threshold as a difference between the affected and unaffected limbs. As such, it does not allow for detection of bilateral

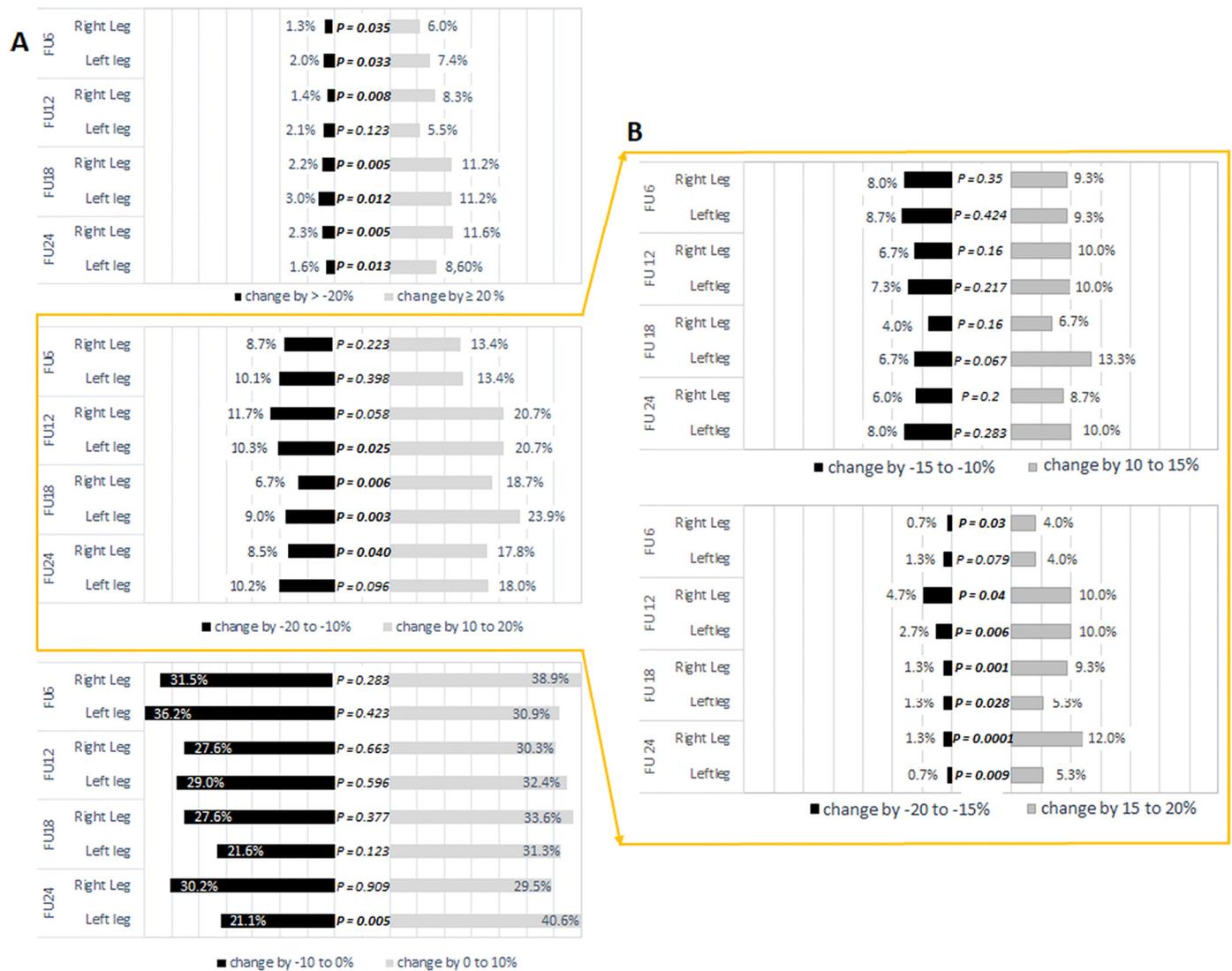


Fig. 2. Comparison of LVC frequency between groups with the equivalent +/- % increment. A: Prevalence of LVC of 0–9%; 10–19%; >20% at individual follow-up visits displayed separately for both legs. B: Subdivision of LVC range 10–19% into 2 subgroups: 10–14%; 15–19%. FU6: six months post-surgery; FU12: 12 months post-surgery; FU18: 18 months post-surgery; FU24: 24 months post-surgery.

LLL, and it does not take into account changes between pre- and post-surgical assessments.

Certain other limitations of the >10% volume increase threshold to determine LLL were previously reported. The LEG study reported LVC >10% in 34% of endometrial cancer patients, but only 18% were diagnosed with LLL when using a multifactorial definition of the morbidity [34]. In our cohort, we observed that volume fluctuations in negative and positive directions occur equally frequently up to a 14% ± increment. These observations suggest that numerous other factors are influencing limb volume up to this threshold. Based on our study, an argument can be made for the threshold for LLL diagnosis to be refined to ≥15% LVC in order to improve the accuracy of diagnosis and warrant better capture of long-term clinically meaningful LLL. It is also supported by the analysis of the relationship of volumetric measurement performed by perometer and patient-reported outcomes which correlated the best with LLL when the ≥15% threshold was applied, reaching a specificity and sensitivity of 56% and 95% [36]. If the ≥15% LVC threshold would be applied to our reported dataset, the overall cumulative incidence of LLL would significantly decrease from 27% to 18%.

Despite its wide-spread use, the tape measurements of circumferential difference has been criticised for not providing an accurate

volumetric assessment of the limb (being reported to overestimate limb volume by 2–8% [37]), and multiple alternative methods have been proposed, including water displacement method, perometry, bioimpedance spectroscopy, and others [13,37,38]. However, in comparison with other LLL assessment methods, tape measurement does not require any specialized equipment nor demanding training, does not carry substantial monetary demands, is safe and well tolerated by patients. With well standardised technique and when performed by appropriately trained operators, an excellent intra-rater reliability can be achieved [39], especially while employing bony landmarks as reference points [40,41]. It was also shown that this method significantly correlates with CT-based volume [42], percentage skin water content [43], and also with bioimpedance spectroscopy measurements [44]. Therefore, assessment of LVC based on tape measurements can provide reliable results when correctly standardised and performed, and for many practical reasons it remains the essential method for large clinical studies.

Another important observation found in our study is a frequent occurrence of transient oedema, which needs to be clearly distinguished from a persistent LLL. Transient periods of lower limb swelling, resolving without intervention within a three-month period, have been

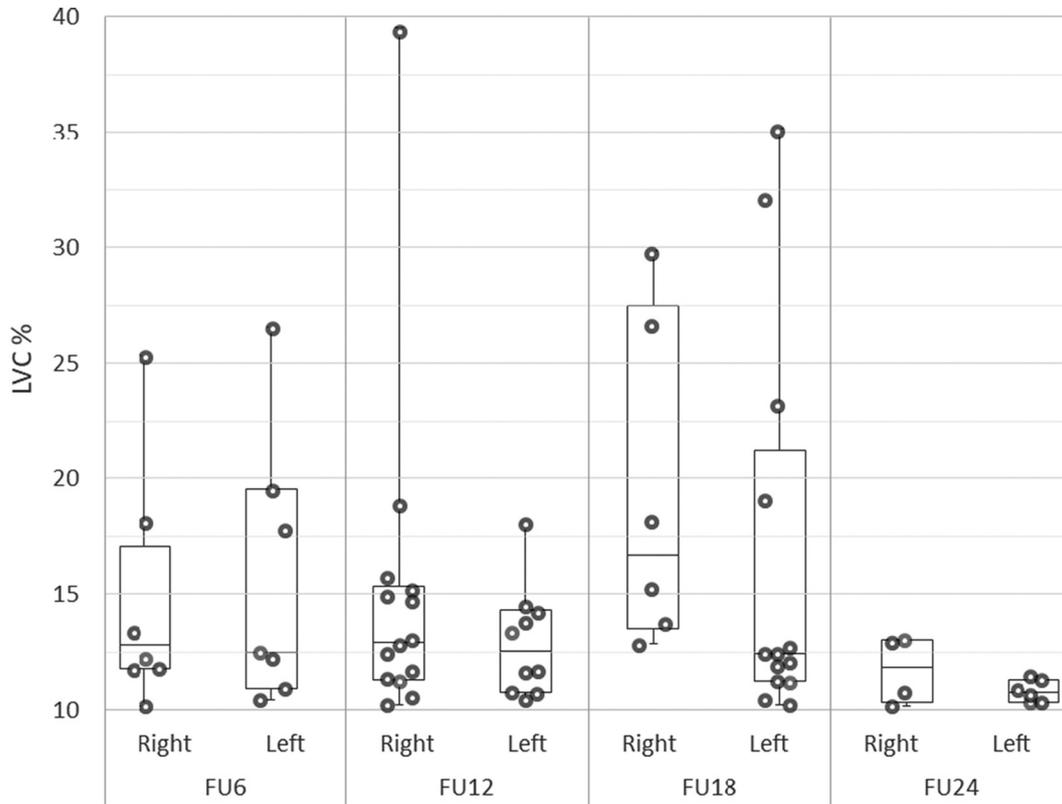


Fig. 3. Incidence of transient oedema. Each dot marks the transient oedema (>10% LVI) of one patient. Boxplots depict the median value of respective transient oedema LVI (%); the percentile range was set at 25% and 50%; the whisker is between minimal and maximal calculated value. FU6: six months post-surgery; FU12: 12 months post-surgery; FU18: 18 months post-surgery; FU24: 24 months post-surgery; LVC: limb volume change.

reported frequently in the first postoperative year after gynaecological cancer treatment [16,45]. Such swelling can be caused by prescribed medication, inflammation, hormonal changes, or other factors such as weight fluctuations, level of physical activity, or even outside temperature [33,46,47]. Obviously, if the LLL assessment is performed only at one time point, such differentiation is not possible. The transitory nature of LVC was previously observed among 541 endometrial cancer patients, in whom 15% experienced two transitions between <10% > LVC and a further 8% experienced more than two transitions

during the 24-month post-surgical follow-up period [34]. In agreement with this observation, 22% of patients in our study experienced transitory oedema at one point during the 24-months of follow-up, with the highest frequency at 12 months post-surgery.

The overall cumulative incidence of LLL is also dependent on the reporting period between the surgery and LLL assessment. Even though the majority of the LLL diagnoses after gynaecological cancer treatment appeared during the first-year post-surgery, a substantial number of cases are observed during the second year of the follow-up [45,48,49].

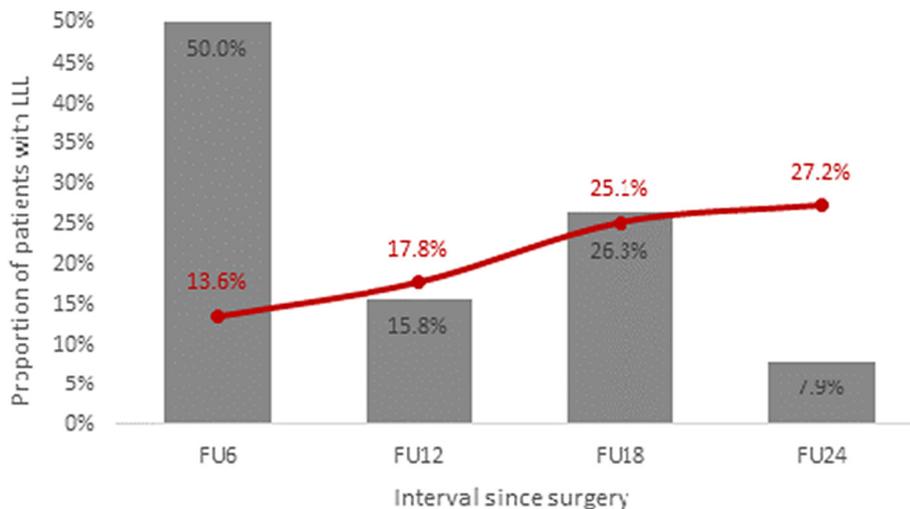


Fig. 4. LLL incidence and onset. Grey columns depict what proportion of patients was diagnosed at individual intervals since surgery. The line shows the cumulative incidence of LLL in the cohort (persistent LVC increase >10%). FU12: 12 months post-surgery; FU18: 18 months post-surgery; FU24: 24 months post-surgery; LVC: limb volume change.



Fig. 5. Detailed analysis of the relationship between limb volume change (LVC) and patient-reported swelling in parts of the limb above and below the knee. The full dots represent the LVC of all individual patients; double circles depict the LVC of patients subjectively reporting oedema in a respective part of the limb; the green line marks LVC 0%; the red line marks LVC 10% increase. A: Above knee; B: Below knee. FU12: 12 months post-surgery; FU18: 18 months post-surgery; FU24: 24 months post-surgery; LVC: limb volume change. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In our study, more than a third of LLL cases were diagnosed after the first year. A limited follow-up period can therefore lead to significant underreporting of the condition.

Finally, we also performed in-depth analysis of the relationship between objective LVC increase and patient-reported swelling. The analysis was performed separately for the subparts of the limb above and below the knee. Surprisingly, subjectively reported symptoms correlated poorly with objective changes. The majority of patients with objective >10% LVC increase did not report subjective swelling, while in up to 50% of patients reporting swelling, we did not find any objective LVC increase. This indicated a low reliability of the subjective assessment. Reliance on self-report also cannot distinguish between the transient swelling events due to other underlying causes and does not necessarily mean that the patient will develop irreversible LLL further on. Therefore, objective measures should always complement patient reporting.

However, it has to be noted that in the assessment of subjective patient-reported swelling we did not employ a validated questionnaire, which contained limb swelling as the only reported LLL symptom, disregarding others, such as heaviness of the limb, numbness, limited mobility and function, or skin changes. Previously published study correlating numerous patient-reported LLL symptoms with result of an objective LLL diagnosis reported that swelling of the limb had relatively low accuracy in LLL prediction, especially when compared to reported numbness and general swelling [50]. Overall, the best accuracy was achieved when the multifactorial assessment was performed and analysed together [50]. It, however, needs to be mentioned that during the study period, no such standardised questionnaire was available or validated in the multiple required languages.

The limitation of our study is the lack of repeated weight measurements for the correlation between BMI changes and LVC fluctuations as only substantial changes in the weight were recorded. However, it was reported that limb volume normalization by the weight changes is not precise for clinical assessments [51]. Another limitation of the study is the lack of control group which does not allow us to compare the results with the outcomes of the healthy population.

5. Conclusions

In conclusion, our study revealed that lower limb volumes after surgical treatment of cervical cancer significantly fluctuate in time and the frequency of fluctuations in positive and negative directions are comparable up to $\pm 14\%$ LVC. Based on these observations and other published reports, a threshold for LLL diagnosis should be increased to $\geq 15\%$, which would, in our case, decrease the cumulative LLL incidence by 9%. Transient oedema is a common phenomenon among the patients, presented in 22% of the whole cohort. A distinction between transient oedema and persistent LLL requires repeated measurements. Since more than a third of new LLL cases are diagnosed in the second year after the surgery, a sufficient follow-up period duration is needed to reliably capture the majority of LLL cases. Finally, we have shown that subjective LLL assessment based on patient-perceived limb oedema correlates poorly with objective LLL diagnosis and should only be used as an adjunct to objective LLL assessment.

Funding

This work was supported by Charles University in Prague (UNCE 204065 and PROGRES Q28/LF1) and by a grant from the Czech Health Research Council (NV19-03-00023). The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Declaration of Competing Interest

None declared.

Acknowledgments

We would like to acknowledge the investigators from all 47 sites participating in the SENTIX trial (Cadron Isabelle, AZ Turnhout, Turnhout, Belgium; Cornez Nathalie, CHU Ambroise Pare, Mons, Belgium; Coronado Martin Pluvio Jesus, Hospital Clinico San Carlos, Madrid, Spain; de Santiago García Francisco Javier, MD Anderson Cancer Center, Madrid, Spain; Dostalek Lukas, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic; Fastrez Maxime, CHU Saint Pierre, Brussels, Belgium; Germanová Anna, Charles University and General University Hospital, Prague, Czech Republic; Van Gorp Toon, University Hospital Leuven, Leuven Cancer Institute, Leuven, Belgium; Haidopoulos Dimitrios, Alexandra Hospital, Athens, Greece; Hryhorenki Andriy, Podiilsky Regional Oncological Centre, Vinnytsia, Ukraine; Kaščák Peter, Faculty Hospital Trenčín, Slovakia; Kridelka Frederic, CHU de Liege, Notre Dame des Bruyeres, Belgium; Kipp Barbara, Lozerner Kantonsspital, Neue Frauenklinik, Switzerland; Landoni Fabio, San Gerardo Hospital, Monza, Italy; van Lonkhuijzen Luc, Academic Medical Center Amsterdam, Netherlands; Luyckx Mathieu, Saint-Luc University Clinics, Brussels, Belgium; Minář Luboš, Masaryk University, Brno, Czech Republic; Novotný Zdeněk, University Hospital in Pilsen, Czech Republic; Ostojich Marcela, Institute of Oncology Angel H Roffo University of Buenos Aires, Argentina; Petiz Almerinda, Instituto Portugues de Oncologia do Porto, Portugal; Ponce Jordi, University Hospital of Bellvitge, Biomedical Research Institute of Bellvitge, (IDIBELL), University of Barcelona, Spain; Raspagliesi Francesco, Fondazione IRCCS Istituto Nazionale Tumori – Milan, Milan, Italy; Redecha Mikuláš, University Hospital, Comenius University, Bratislava, Slovakia; Sánchez Octavio Arencibia, University Hospital of the Canary Islands, Las Palmas de Gran Canaria, Spain; Sehnal Borek, University Hospital Bulovka, First Faculty of Medicine, Charles University, Prague, Czech Republic; Smrkolj Spela, University Medical Centre Ljubljana, Ljubljana, Slovenia; Staringer Juan Carlos, Hospital Español de Buenos Aires, Caba, Argentina, and Hospital de Alta Complejidad de Formosa, Formosa, Argentina; Tamussino Karl, Medical University of Graz, Graz, Austria; Tingulstadt Solveig, Trondheim University Hospital, Norway; Tummers Philippe, University Hospital Gent, Belgium; Valha Petr, Hospital České Budějovice, Czech Republic; Zalewski Kamil, Holycross Cancer Center, Kielce, Poland; Zorrero Cristina, Instituto Valenciano de Oncologia (IVO), Valencia, Spain); and members of the Steering Committee (Dusek Ladislav, Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic; Kucukmetin Ali, Northern Gynaecological Oncology Centre, Queen Elizabeth Hospital, Gateshead, UK; Querleu Denis, Institut Bergonie, Bordeaux, France; van der Zee Ate, University Medical Center, Groningen, Netherlands). We also thank all the medical specialists, data and case managers, secretaries, study coordinators, and other people involved in the SENTIX trial.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ygyno.2021.10.089>.

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