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## Occurrence and prognosis of lymph node metastases in patients selected for isolated limb perfusion with soft tissue sarcoma

Crettenand François

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**UNIVERSITÉ DE LAUSANNE - FACULTÉ DE BIOLOGIE ET DE MÉDECINE**

DÉPARTEMENT DES SERVICES DE CHIRURGIE ET D'ANESTHÉSIOLOGIE

SERVICE DE CHIRURGIE VISCÉRALE

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**Occurrence and prognosis of lymph node metastases in patients selected for isolated limb perfusion with soft tissue sarcoma.**

THESE

préparée sous la direction du Professeur Maurice Matter

et présentée à la Faculté de biologie et de médecine de  
l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

François Olivier Christophe Crettenand

Médecin diplômé de la Confédération Suisse  
Originaire de Iséables (Valais)

Lausanne  
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# Imprimatur

*Vu le rapport présenté par le jury d'examen, composé de*

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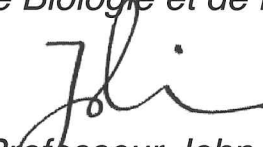
**Monsieur François CRETENAND**

*intitulée*

***Occurrence and prognosis of lymph node metastases in patients  
selected for isolated limb perfusion with soft tissue sarcoma***

*Lausanne, le 20 septembre 2018*

*pour Le Doyen  
de la Faculté de Biologie et de Médecine*



**Monsieur le Professeur John Prior  
Vice-Directeur de l'Ecole doctorale**

**Incidence et pronostic des métastases ganglionnaires chez les patients atteints d'un sarcome de membre et sélectionnés pour un traitement par perfusion isolée de membre.**

**Occurrence and prognosis of lymph node metastases in patients selected for isolated limb perfusion with soft tissue sarcoma.**

François Crettenand, David Martin, Stéphane Cherix, Nicolas Demartines et Maurice Matter.

*Objectifs:* Chez les patients atteints de sarcome des membres (inférieur ou supérieur) une chirurgie radicale et étendue est souvent nécessaire. Au début des années 80, une nouvelle approche a été développée : la perfusion isolée des membres (isolated limb perfusion-ILP en anglais). La présente étude a été conçue afin d'évaluer l'incidence et l'impact sur la survie des métastases ganglionnaires découvertes chez ces patients sélectionnés pour une ILP avec curage ganglionnaire associé.

*Méthode:* Il s'agit d'une étude rétrospective de 57 patients chez qui l'on a réalisé une perfusion isolée du membre en raison d'un sarcome des tissus mous. Durant l'abord chirurgical un curage ganglionnaire a été réalisé de manière systématique pour l'abord vasculaire et un bilan ganglionnaire. Ces patients ont tous été opérés au CHUV entre 1992 et 2015.

*Résultats :* L'âge médian des patients était de 62 ans (19-87), 30 patients étaient de sexe masculin (53%). Une atteinte ganglionnaire a été mise en évidence chez 13 patients (N1, 23 %). Parmi les types histologiques représentés, on retrouve 4 angiosarcomes, 3 sarcomes épithélioïdes, 2 léomyosarcomes, 2 sarcomes synoviaux ainsi que 2 sarcomes indifférenciés. Lorsque l'on étudie la survie entre les deux groupes, on retrouve une survie médiane de 73,9 mois (CI 95% 41.9-105.9) chez les patients n'ayant pas d'atteinte ganglionnaire, contre 15,1 mois (CI 95% 7.4-22.6) en cas d'atteinte des ganglions ( $p=0.002$ ). La survie sans maladie est quant à elle de 33,0 mois (CI 95% 12,5-53.5) chez les patients sans atteinte ganglionnaire. Elle s'effondre à 8,0 mois (CI 95% 4.0-11.9) en cas de dissémination de la maladie au niveau des ganglions ( $p=0.006$ ).

*Conclusions :* Les métastases ganglionnaires chez les patients atteints d'un sarcome des tissus mous et sélectionnés pour une perfusion isolée du membre semblent avoir un impact majeur sur la survie sans maladie et la survie globale. Un curage ganglionnaire doit être réalisé lorsque l'on réalise une perfusion isolée du membre. Pour les autres patients atteints de sarcome et selon le type histologique, une atteinte ganglionnaire devrait être suspectée et le cas échéant un curage ganglionnaire discuté.

Research Paper

# Occurrence and prognosis of lymph node metastases in patients selected for isolated limb perfusion with soft tissue sarcoma

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## Abstract

**Background and Objectives:** Extensive surgery is often required for advanced soft tissue sarcoma (STS) of the limb. In the 1980s, a new approach was developed: isolated limb perfusion (ILP). This study aimed to assess incidence and impact on patient survival based on lymph node metastasis with systematic radical lymphadenectomy during ILP.

**Methods:** Retrospective study of 57 consecutive patients treated by ILP for limb STS with simultaneous radical lymph node dissection in our tertiary referral center between 1992 and 2015.

**Results:** Median age was 62 years (19-87) and 30 patients were male (53%). Lymph node involvement was observed in 13 patients (N1, 23%), regarded as metastatic spreading in 4 angiosarcomas, 3 epithelioid sarcomas, 2 leiomyosarcomas, 2 undifferentiated sarcomas and 2 synovial sarcomas. For the N0 patient group, median survival was 73.9 months (CI 95% 41.9-105.9) compared to 15.1 months (CI 95% 7.4-22.6) in case of metastatic lymph node ( $p=0.002$ ). The median disease-free survival was 33.0 months (CI 95% 12.5-53.5) in N0 group and 8.0 months (CI 95% 4.0-11.9) in N1 ( $p=0.006$ ).

**Conclusions:** Lymph node metastases of STS patients selected for ILP seemed to have a negative impact on both overall and disease-free survival. Radical lymph node dissection should be included in ILP procedure.

Key words: limb sarcoma, lymph node metastases, incidence, prognosis

## Introduction

Soft tissue sarcomas (STS) are tumours arising from connective tissues, with an incidence of about 5 per 100'000 [1]. Their prognostic is poor, with an overall 50% 5-year survival [2, 3]. Previously, limb STS were treated by amputation until 1982 when a randomised controlled trial that showed no benefit regarding overall survival (OS) when amputation was compared to limb-sparing resection plus adjuvant radiation therapy [4]. The Isolated Limb Perfusion technique (ILP) was first described in 1958 [5]. The technique has been increasingly used since 1992, when a 90 % remission rate for STS treated by a combination of chemotherapy and Tumour Necrosis

Factor alpha (TNF $\alpha$ ) has been demonstrated [6]. More recently, a review has shown that ILP was an acceptable modality for neoadjuvant treatment of limb STS initially regarded as unresectable [7]. Three decades ago, former studies have retained that there was no indication for systematic radical lymph node dissection even in case of locally advanced disease [8-10]. Despite an increasing interest for radical lymph node dissection as part of treatment for sarcomas, there is currently no study on a standardized population in which radical lymph node dissection was performed systematically.

The study aim was to assess incidence and impact on patient survival of lymph node metastases in limb STS during ILP with systematic radical lymphadenectomy.

## Patients and Methods

### Patients

Retrospective study including all consecutive patients treated by ILP for limb STS with systematic radical lymph node dissection in our tertiary referral centre between 1992 and 2015. Distant metastasis at diagnosis was not an exclusion criterion. Extracted data from medical files included demographics, surgical reports, radiological findings, pathological reports and follow-up. Some patients received neoadjuvant chemotherapy and/or radiotherapy according to local protocols, while others benefited from primary ILP.

### Isolated Limb Perfusion (ILP)

The details of surgical technique have been widely published [6, 11-13]. In brief, the external iliac, the femoral or axillary artery and vein respectively of the diseased limbs are clamped, cannulated and connected to an extracorporeal circuit. In our centre, a radical ilio-inguinal or axillary lymph nodes dissection was systematically performed during vascular dissection to optimize vascular access. To minimize the risk of chemotherapy leakage, the collateral vessels were ligated and a tourniquet applied at the root of the limb. The limb was heated and maintained at a temperature between 38° and 40° Celsius. Leaks were assessed with human albumin radiolabelled by Tc99m and a gamma camera placed in precordial position [14]. Once rheological parameters were adjusted and stable, a single dose of Melphalan (Alkeran® - Pro Concepta Zug AG Switzerland) of 13 mg/l for upper limb and 10 mg/l for lower limb was perfused. At the same time, from 1 to 4 mg of recombinant Tumour Necrosis Factor alpha (Beromun® Boehringer-Ingelheim GmbH Ingelheim Germany) was added [15]. After 60 minutes of perfusion, the limb was rinsed with up to 4 litres of saline solution then the systemic circulation restored.

### Radical lymph node dissection

Pelvic radical lymph node dissections (RNLD) included external iliac and obturator lymph nodes. Axillary RLND included level I - III dissection. In this study, RNLD was performed regardless of clinical or radiological lymph node status.

### Tumour and staging

The histologic grading system used was the FNCLC (Fédération National des Centres de Lutte

contre le Cancer) [16, 17].

### Statistical analysis

Quantitative variables were presented as mean (standard deviation) and compared with Mann-Whitney U test. Qualitative variables were presented as frequencies (percentage) and compared with Pearson's chi-square or Fisher's exact test as appropriate. The OS was calculated from the date of ILP until patient's death or last follow-up. The disease-free survival was calculated from ILP until local recurrence or metastases documented by MRI or CT-scan (regular follow-up every 3 months with clinical work up and imaging). Patients with initial distant metastases were excluded from the disease-free survival analysis. The survival curves were drawn according to Kaplan-Meier's method with a Log Rank test (Mantel-Cox) to compare groups. A p value  $\leq 0.05$  was considered statistically significant. All statistical analyses were performed using SPSS 23.0 software (SPSS Inc., Chicago, IL).

### Ethics

The study was conducted according to the Declaration of Helsinki principles of good clinical practice and approved by the Local Ethics' Committee (Protocol number 392/11).

### Results

Fifty-seven patients had ILP with radical lymph node dissection for limb STS. Four patients had a second ILP and only the first intervention was considered. Median age was 62 years (range 19-87, SD 17.3) and 30 patients were male (53%). Seven patients had upper limb (12%) and 50 lower limb (88%) STS. Only 4 patients had synchronous distant metastases (3 with lung and 1 with liver metastases). The various histological types of sarcomas are described according to lymph node involvement in **Table 1**.

**Table 1.** Histology of sarcomas and lymph node involvement

	N-positive n=13	N-negative n=44	Total n=57
Angiosarcomas	4	3	7
Epithelioid sarcomas	3	1	4
Leiomyosarcomas	2	3	5
Synovial sarcomas	2	2	4
Undifferentiated sarcomas	2	8	10
Liposarcomas	0	13	13
Pleiomorphic sarcomas	0	5	5
Neurofibrosarcoma	0	2	2
Clear cell sarcoma	0	1	1
Osteosarcoma	0	1	1
Desmoid tumour	0	1	1
Unclassified subtypes	0	4	4

Mean number of resected lymph node was 9.5 (range 1-41, SD 7.2). Lymph node metastatic disease

was observed in 13 patients (N1, 23%): 4 angiosarcomas, 3 epithelioid sarcomas, 2 leiomyosarcomas, 2 undifferentiated sarcomas and 2 synovial sarcomas. No statistically significant correlation was found between tumour size, location and development of nodal metastasis (Table 2). In terms of tumour grades, patients with nodal involvement (N1) had significantly more grade 3 compared to N0 group (69% vs. 32%, p=0.019).

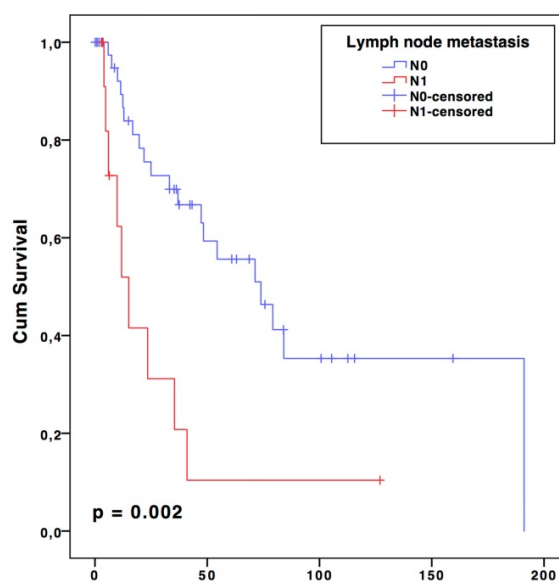
**Table 2.** Oncological properties of sarcomas and lymph node involvement

	N-positive n=13	N-negative n=44	P-value
Mean tumour size in cm (SD)	10.6 (5.1)	10.1 (6.1)	0.627
Tumour grade, n (%)			
G1	0	3 (7)	0.453
G2	4 (31)	27 (61)	0.052
G3	9 (69)	14 (32)	<b>0.019</b>
Tumour localisation, n (%)			
Upper limb			0.643
Proximal	1 (8)	4 (9)	
Distal	1 (8)	2 (5)	
Lower limb			0.161
Proximal	8 (61)	19 (43)	
Distal	3 (23)	19 (43)	

For the N0 patient group, median survival was 73.9 months (CI 95 % 41.9-105.9) compared to 15.1 months (CI 95 % 7.4-22.6) in case of metastatic lymph node(s) (N1) (p=0.002, Fig. 1). Median disease-free survival was 33,0 months (CI 95% 12,5-53.5) in N0 group and 8.0 months (CI 95% 4.0-11.9) in N1 (p=0.006, Fig. 2). There was no significant overall or disease-free survival between histological types, although the small number of cases limited the analysis.

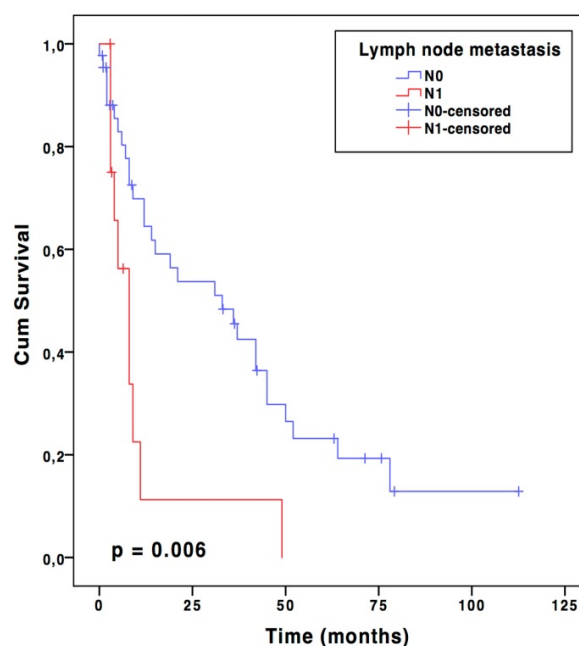
### Discussion

This present study is one of the few that adopted systematic lymph node resection during ILP. Lymph node involvement was found in 23% of patients, which is slightly higher than what was usually published: nodal metastasis rate in the literature varies between 1,3 % and 24,7 % according to studied populations and histological subtypes [9, 10, 18-21]. However, a recently published retrospective study of patients with STS showed that nodal metastasis rates for STS histologic subtypes were higher than previously reported. This discrepancy could be explained by the absence of standardized lymph node evaluation among patients who underwent surgery for STS. According to other studies, RLND was performed only when lymph drainage area was included in resection's margins [9, 21]. Moreover, other authors considered RLND only in patients with preoperative evidence of lymph nodes metastases [18].



	Patients at risk				
	0	50	100	150	200
N0	44	16	6	2	0
N1	13	1	1	1	1

**Figure 1.** Overall Survival



	Patients at risk				
	0	25	50	75	100
N0	41	20	9	4	1
N1	12	1	0	0	0

**Figure 2.** Disease-free survival



In the present study, lymph node metastases of STS seemed to have a negative impact on both OS and disease-free survival. There was a significant decline of 59-months in overall survival for patients with lymph node involvement. There was also a 37-month difference in disease-free survival. Lymph node involvement appeared to be a factor that clinically reflects the biological aggressiveness of the tumour [18, 21]. It is interesting to note that despite the negative impact of lymph node involvement, the American Joint Committee on Cancer (AJCC) revised its impact on survival. Indeed, in the two last cancer staging manual editions (2010 and 2016) N1 sarcomas were classified as stage III and no longer as stage IV compared to the 2002 version [22]. Stage IV now includes only distant metastatic patients. Lymph node involvement alone is not as aggravating as distant metastases in term of prognosis [21]. The OS benefit offered when the tumour did not reached the lymph nodes in addition together with potentially curative aspect of RLND are major arguments in favour of systematic lymph node dissection during ILP [23]. Moreover, the benefits of this treatment appear to be higher than its potential morbidities (lymphedema, lymphocele, infection and hematoma) [24]. The results from the present study suggest that lymph node dissection should be done systematically at least when an ILP procedure is performed. However, this cannot be claimed for sarcomas in general.

Given the potential benefit of recognizing and removing occult lymph node involvement, some centres proposed to search sentinel node in patients with STS. Recently, a prospective study demonstrated the safety and accuracy of sentinel lymph node biopsy compared to PET-CT to identify therapy-changing nodal disease [25]. However, a meta-analysis recommended sentinel lymph node biopsy prior to radical lymphadenectomy only in sarcoma subtypes with a high risk of lymph node involvement [20]. A retrospective study of an American National Cancer Data Base identified that nodal metastasis rates were highest among patients with rhabdomyosarcoma (32.1%), angiosarcoma (24.1%), clear cell sarcoma (27.7%), and epithelioid sarcoma (31.8%), which is similar to this series as well as another retrospective study [9, 26]. From the anatomical point of view, it has been shown that proximal-type sarcomas have significantly more aggressive clinicopathological features, particularly lymph node metastasis [27]. Regarding tumour grade, high grade sarcomas tend to have lymph node metastases (69%), as previously reported by some authors in retrospective studies [26, 28]. The fact that some STS subtypes are at high risk for nodal involvement should be included in treatment planning. For sarcomas with potentially

high lymph node involvement risk, an active detection of lymph node metastases may be evaluated preoperatively (sentinel lymph node biopsy, MRI/CT or PET-CT) [29]. Unfortunately, given the small number of patients in the present series, conclusions and recommendations cannot be drawn for "high-risk" histologies. In the absence of clear recommendations, systematic lymph node dissection during ILP is performed in our academic center. However, according to results of this series and other retrospective studies, it could be considered to perform a RLND for high risk sarcomas (rhabdomyosarcoma, angiosarcoma, clear cell sarcoma, epithelioid sarcoma, synovial sarcoma) and not only during ILP procedures [26, 29].

Conventional imaging modalities (CT-scan and MRI) show a poor sensitivity (small nodal metastases) and specificity (inflammation) for the detection of lymph node metastases. On contrary,  $^{18}\text{F}$ -FDG-PET has proven to be a promising imaging modality for detecting primary tumours, lymph node metastases and bone involvement of sarcomas, with better sensitivity than conventional methods including ultrasound and bone scintigraphy [30]. Another previously published study estimated a positive predictive value for lymph node metastasis of 27% [31]. In addition,  $^{18}\text{F}$ -FDG-PET can also be used in the evaluation and monitoring of tumour response to therapy. Nevertheless, a discrepancy in 42.9% of cases between the pathological evaluation and that obtained by PET has been described [32].

The main limitation of the present study is its retrospective nature and a relatively small number of patients that prevented multivariate analysis. Furthermore, a wide range of histological subtypes was included. On the other hand, sarcoma is an orphan disease among adult and paediatric populations. Currently, the lack of clear recommendations regarding lymphadenectomy in STS probably leads to an underestimation of lymph node metastases rate and its impact on patient's mortality. Moreover, the same limit applies to neoadjuvant treatments, because there is currently no clear accepted protocol. More research is needed to make evidence-based recommendations in favour of systematic radical lymph node dissection as part of the surgical treatment. The definitive role of RLND in ILP's for limb sarcoma patients' needs more studies.

In conclusion, lymph node metastases of soft tissue sarcoma patients selected for regional therapy (ILP) seemed to have a negative impact on both overall and disease-free survival. Systematic radical lymph node dissection should be included in ILP procedures to have more precise diagnosis with possible positive impact on outcome.

## Note

This paper was presented in parts as a poster to the Annual Meeting of the Swiss Society of Visceral Surgery (SSCV), September 2017, Lausanne, Switzerland.

## Competing Interests

The authors have declared that no competing interest exists.

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