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Isolated lymph node recurrence in epithelial ovarian cancer: recurrence with better prognosis?

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ABSTRACT

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Introduction: The aim of this study was to compare overall survival (OS) between women with isolated lymph node recurrence (ILNR) and those with isolated peritoneal localization of recurrence (ICR), in patients managed for epithelial ovarian cancer.

Methods: Data from 1,508 patients with ovarian cancer were collected retrospectively from1 January 2000 to 31 December 2016, from the FRANCOGYN database, pooling data from 11 centres specialized in ovary treatment. Median overall survival was determined using the Kaplan-Meier method. Univariate and multivariate analyses were performed to define prognostic factors of overall survival. Patients included had a first recurrence defined as ILNR or ICR during their follow up.

Results: 79 patients (5.2%) presented with ILNR, and 247 (16.4%) patients had isolated carcinomatosis recurrence. Complete lymphadenectomy was performed more frequently in the ILNR group vs. the ICR group (67.1% vs. 53.4%, p=0.004) and the number of pelvic lymph nodes involved was higher (2.4 vs. 1.1, p=0.008). The number of involved pelvic LN was an independent predictor of ILNR (OR = 1.231, 95% CI [1.074-1.412], p = 0.0024). The 3-year and 5-year OS rates in the ILNR group were 85.2% and 53.7% respectively, compared to 68.1% and 46.8% in patients with ICR. There was no significant difference in terms of OS after initial diagnosis (p = 0.18). 3- year and 5-year OS rates after diagnosis of recurrence were 62.6% and 15.6% in the ILNR group, and 44% and 15.7% in patients with ICR (p = 0.21).

Conclusion: ILNR does not seem to be associated with a better prognosis in terms of OS.

Key words: epithelial ovarian cancer, recurrence, isolated lymph node recurrence, isolated carcinomatosis recurrence, prognosis, overall survival

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INTRODUCTION

Epithelial ovarian cancer (EOC) ranks seventh in terms of incidence among women's cancer, with 295,414 new cases and 184,799 cases of specific mortality in 2018 worldwide[1]. EOC is primarily a disease found in postmenopausal women. In fact, diagnosis and death after 55 years represent approximately 70% and 85% of cases respectively[2,3].

Unlike many other cancers, EOC is often diagnosed at an advanced stage because of non specific symptomatology which progresses very gradually[4–6]. The prognosis is poor, with an overall average survival at 5 years of 45% for all types and all stages combined, and 25% for cancer discovered at stage III / IV for all types[3,5,7]. It is acknowledged that a patient with a malignant tumour of the ovary will die in 80% of cases as a result of her disease[3].

The pattern of recurrence of EOC after primary treatment has been extensively investigated by several authors who agree that most recurrences occur within 2 years of diagnosis, and that most deaths are a result of uncontrolled disease [8–10].

The pattern of dissemination is either locoregional (vaginal or pelvic recurrence most likely a peritoneal carcinomatosis), distant (pleural involvement, liver, lung, lymph nodes and brain) or a combination of both [3–5,7]. However, the optimal treatment strategy for women with recurrent disease remains somewhat vague as most published studies are retrospective with a relatively low number of patients [2–7,11, 12]00/00/0000 00:00:00.

Among those events, Isolated Lymph Node Recurrence (ILNR) is a rare event in the context of EOC since it affects only 1 to 6% of cases, localized, in order of frequency, in the para-aortic LN, pelvic LN, inguino-femoral LN and the axillary LN[13,14].
Existing studies underline a better prognosis in terms of treatment responses and survival after ILNR[13–20]. However, in this specific setting the comparison of such recurrence with another location, particularly in the form of isolated carcinomatosis has not been reported.

Hence, the objective of this study was to compare overall survival (OS) between women with isolated lymph node recurrence (ILNR) and those with isolated peritoneal localization of recurrence (ICR).

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MATERIALS & METHODS

We conducted a retrospective, descriptive, multi-centre study. Data from 1,508 women with ovarian cancer collected from 1 January 2001 to 31 December 2016 were reviewed from the FRANCOGYN database pooling data from 11 centres: "Centre Hospitalier Universitaire, Tours", "Hôpital de Tenon" in Paris, "Centre Hospitalier Universitaire, Rennes", "Centre Hospitalier Universitaire, Strasbourg", "Centre de Lutte Contre le Cancer Georges François Leclerc" in Dijon, "Centre Hospitalier Intercommunal, Créteil", "Hospices Civils de Lyon", "Centre Hospitalier Jean Verdier" in Paris, "Centre Hospitalier de la Pitié-Salpêtrière" in Paris, "Centre Hospitalier Universitaire, Lille", and "Centre Hospitalier Poissy".

Patients included had a first recurrence defined as ILNR or isolated peritoneal recurrence during their follow-up.

Exclusion criteria included absence of surgical management or chemotherapy at primary diagnosis, absence of recurrence during follow-up, other recurrence locations (extra-peritoneal and non-lymph node location), or unavailable data.

After completion of platinum-based chemotherapy patients were followed every 3-4 months with a review of clinical symptoms, a physical examination, CA 125 test and imaging according to symptoms.

Recurrence was diagnosed where there were clinical signs of the disease, an increase in the CA125 test result at successive examinations according to the "Gynecological Cancer Intergroup"[21] criteria and / or where suspicious images were discovered during radiological follow-up according to the RECIST criteria[22]. ILNR and isolated peritoneal recurrence were respectively defined as recurrence, the localization of which only involved a lymph node region (ILNR) or the peritoneum (ICR), objectified by an imaging assessment involving at least a CT-scan and/or PET scan, and confirmed or not by a surgery/histological samples. For each case, data were collected through medical records. Histological data were collected from computerized histological reports. The imaging data were collected from the computerized reports of the examinations.

The various statistical analyses were carried out using the R™ software version 3.5.1 (R Stat). Continuous variables were compared using a Mann-Whitney test or a Student's test based on

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enrolment size. Categorical variables were compared using Fisher's exact test or chi-2 test based on the size of the sample. The statistical significance threshold used was $p < 0.05$.

The factors associated with the type of recurrence were analysed by logistic regression on all variables with p-value of <0.10 in univariate analysis. A bilateral formulation was chosen for all tests. The Odds Ratios (ORs) are given with their 95% confidence interval.

Overall survival (OS) curves were produced using the Kaplan-Meier method. OS time (in months) was calculated as the time between the initial diagnosis of ovarian cancer and the date of death.

Survival was compared by univariate analysis by log-rank and multivariate analysis by Cox logistic regression. The Hazard Ratios (HRs) are given with 95% confidence intervals.

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RESULTS

During the study period, 1,508 patients with EOC were treated in the 11 FRANCOGYN research group centres. Among these patients, 79 (5.2%) presented with ILNR, and 247 (16.4%) patients with isolated carcinomatosis recurrence. Table 1 reports the demographic characteristics for these patients.

Table 1: Characteristics of the population with Isolated Lymph Node Recurrence (ILNR, n=79) and Isolated Carcinomatosis Recurrence (ICR, n=247)

Demographic characteristics	**ILNR (n=79)**	**ICR (n=247)**	**p**
	n (%)	**n (%)**	
Age at diagnosis (years)	60 ± 10.9 [36-84]	60.3 ± 12.4 [20-92]	0.88
Body Mass Index (kg/m²)	24.6± 6.1 [16.3-44.9]	24.9± 4.8 [13.5-42.3]	0.70
Post Menopausal	65 (82.2)	191 (77)	0.77
Nulliparity	14 (17.7)	64 (26)	0.68
Personal history of breast cancer	7 (8.9)	11 (4.5)	0.20
Familial history of ovarian cancer	7 (8.9)	11 (4.5)	0.16
Genetic predisposition			
BRCA1	9 (11.4)	14 (5.7)	<0.0001
BRCA2	2 (2.5)	3 (1.2)	
Tumour histology			0.22
High grade serous	55 (69.6)	146 (59.1)	
Low grade serous	5 (6.3)	13 (5.3)	
Serous NA	5 (6.3)	19 (7.7)	
Undifferentiated	4 (5)	24(10)	
adenocarcinoma	4 (5)	15 (6.1)	
Clear cells	2 (2.5)	15 (6.1)	
Endometrioid	3 (3.8)	3 (1.2)	
Mucinous	1 (1.3)	5 (2)	
Serous & endometrioid	?	5(2)	
Carcinosarcoma			
Lymphovascular emboli	13 (16.5)	47 (19)	1
Initial FIGO stage			0.62
Stage I	5 (6.3)	18 (7.3)	
Stage II	3 (3.8)	9 (3.6)	
Stage III	57 (72.2)	188 (76.1)	
Stage IV	14 (17.7)	30 (12.1)	
CA125 (mg/L) at initial diagnosis	1596 ± 2381[8-12400]	1804 ± 2381[8-48000]	0.85

Data are presented by mean ± standard deviation [1st quartile - 3rd quartile] or numbers (%) / FIGO: International Federation of Gynecology and Obstetrics

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The characteristics of initial management of these patients are summarized in Table 2. For ILNR: 36 (45.6%) had lymph node involvement during initial management, of which 23 patients (29.1%) had pelvic lymph node involvement and para-aortic involvement at the same time.

For ICR: 84 (34%) had lymph node involvement during initial management, of which 40 patients (47.6%) had pelvic lymph node involvement and para-aortic involvement at the same time.

Treatment of ILNR included chemotherapy alone for 52 (65.7%) patients, surgery alone for 2 (2.5%) patients, the combination of surgery followed by chemotherapy for 17 (21.5%) patients and the combination of chemotherapy and radiotherapy for one patient (1.3%). Treatment of ICR included chemotherapy alone for 207 (83.8%) patients, the combination of surgery with chemotherapy for 40 (16.2%).

Table 2: Initial management of patients with isolated lymph node recurrence (n=79) and isolated carcinomatosis recurrence

Characteristics	ILNR (n=79) n (%)	ICR (n=247) n (%)	p
Primary cytoreduction surgery	31 (39.3)	91 (36.8)	0.89
Cytoreduction surgery after neoadjuvant chemotherapy	48 (60.7)	156 (63.2)	0.91
Tumour residue			0.22
No residue	50 (63)	166 (67.2)	
Residue <10 mm	9 (8.8)	24 (9.7)	
Residue >10 mm	18 (22.7)	42 (19)	
Unknown residue	2 (2.5)	15 (6.1)	
Type of lymphadenectomy			**0.004**
No lymphadenectomy	17 (21.5)	82 (33.2)	
Complete lymphadenectomy (PA et pelvic)	53 (67.1)	132 (53.4)	
Pelvic lymphadenectomy alone	5 (6.3)	3 (1.2)	
Para-aortic lymphadenectomy alone	3 (3.8)	22 (8.9)	
Lymph node involvement	36 (45.6%)	84(34)	0.21
Pelvic lymphadenectomy performed	58 (74.7)	135 (54.7)	0.004
Pelvic lymph node invasion	29 (36.7)	49 (19.8)	0.21
Number of invaded pelvic lymph nodes	2.4 ± 3.2 [0-12]	1.1 ± 1.8 [0-12]	**0.01**
Para-aortic lymphadenectomy performed	56 (73.3)	154 (62.3)	0.29
Para-aortic lymph node invasion	30 (38)	75 (30.4)	0.23
Number of invaded para-aortic lymph nodes	3.25 ± 4. [0-20]	2.5 ± 4.8 [0-37]	0.42
Time to recurrence			0.14
Sensitive to platinum	46(58.2)	108(43.7)	
Intermediate sensitivity	21(26.6)	77(31.2)	
Resistant to platinum	11(13.9)	48(19.4)	
Unknown	1(1.3)	14(5.7)	

Data are presented by mean ± standard deviation [1st quartile - 3rd quartile] or numbers (%) /
PA: Para-aortic

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Both groups were comparable in terms of initial surgical treatment and tumour residue. There was a difference between the two groups with regard to the LN surgery performed. In fact, the proportion of complete lymphadenectomy performed was higher in the ILNR group (p=0.004). There was no difference in the proportion of patients with lymph node involvement between the two groups (p=0.21), however, there were more metastatic pelvic LN in the ILNR group compared with the ICR group (2.4 vs. 1.07; = 0.01). This difference did not affect the mean number of affected para-aortic LN in both groups (3.25 vs. 2.53, p = 0.42). Time to first recurrence was comparable between groups (p. = 0.14).

Median RFS for patients with ICR was 22 months (range 1-355 months) and was not statistically different from RFS in patients with ILNR (p=0.51).

Predictors of type of recurrence:

The univariate logistic regression analysis looking for predictors of one of the two forms of recurrence found that the type of lymphadenectomy (p = 0.0062), in particular complete lymphadenectomy (OR = 1.937, 95% CI [1.05-3.57]) and performing pelvic lymphadenectomy alone (OR = 8.039 95% CI [1.75-36.89]) were predictors of ILNR. Similarly, whether or not pelvic lymphadenectomy was performed independently of a para-aortic procedure (OR = 2.352, 95% CI [1.32-4.91], p = 0.0026) and the mean number of pelvic LN involved (OR = 1.245). 95% CI [1.085-1.428], p = 0.0013) predicted ILNR. In the multivariate analysis, only the number of involved pelvic LN was an independent predictor of ILNR (OR = 1.231, 95% CI [1.074-1.412], p = 0.0024).

Overall survival:

The 3-year and 5-year OS rates in the ILNR group were 85.2% and 53.7% respectively, compared to 68.1% and 46.8% in patients with ICR. There was no significant difference in terms of OS after initial diagnosis of EOC (p = 0.18) Figure 1.

3- year and 5-year OS rates after diagnosis of recurrence were 62.6% and 15.6% in the ILNR group, and 44% and 15.7% in patients with ICR (p = 0.21).

Despite the absence of a significant difference, the survival curves (Figure 2) suggest that in the first three years following the initial diagnosis and the diagnosis after recurrence, the OS rate is better in the ILNR group before it merges with that of patients with ICR after 5 years, after which time it is similar.

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DISCUSSION

In our study, ILNR occurred in 5.2% of the overall EOC population. These data are consistent with those of the literature, which found a proportion of between 4.2% and 6.1% of all EOC cases. The proportion of patients experiencing recurrence in the form of isolated carcinomatosis was 16.4%. No other data is available in the current literature.

In this study, the 3-year and 5-year OS rates in ILNR were 85.2% and 53.7% respectively, compared to 68.1% and 46.8% in patients with ICR. There was no significant difference in terms of OS after initial diagnosis of EOC. 3-year and 5-year OS rates after the diagnosis of recurrence were 62.6% and 15.6% in the ILNR group, and 44% and 15.7% in patients with ICR ($p = 0.21$).

Our study is the first to compare the survival of patients with ILNR compared to those with recurrence as isolated carcinomatosis from the same population. ILNR is intuitively considered as being associated with a favourable prognosis without any literature data to support this assumption.

To the best of our knowledge, the difference in survival between women with lymph node involvement and peritoneal carcinomatosis has only been evaluated during initial management of the disease. Gasimli *et al.*[23] showed a significant difference in 5-year OS in a FIGO stage III EOC population according to initial tumour spread between patients with LN involvement only, compared to patients with tumour spread to the peritoneum only (91.7 vs. 47.4%, $p < 0.01$).

Comparison of survival did not find any significant difference either after the initial diagnosis or after the diagnosis of recurrence. 5-year OS rates after the initial diagnosis were similar for both groups. However, it should be noted that the kinetics of survival curves differed between these two groups. The 3-year OS rates are better in the ILNR group compared to the group of ICR patients, both after initial diagnosis and after recurrence. This could indicate the existence of a slowly progressive form of localized recurrence in the lymphatic tissue with secondary progression towards peritoneal and / or a distant dissemination. Indeed in Blanchard's study[17], simple monitoring was possible during 12 to 18 months after ILNR for seven patients (23%). The median OS was 91 months for this subgroup.

Gadducci *et al.*[13] demonstrated that treatment of ILNR (surgery and chemotherapy vs. chemotherapy) was an independent factor influencing Recurrence-Free-Survival (HR = 0.277, p = 0.0003) and OS (HR = 0.249, P = 0.0002). In the study by Ferrero *et al.*[14], complete secondary cytoreduction was performed for 71 of the 72 patients in the study, and OS at 5

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years after treatment of recurrence reached 61%. It is the same in the study by Uzan *et al.*[16] in which the 12 patients had received secondary cytoreduction with a 5-year OS of 71% after treatment of recurrence. However, the populations in these studies are not comparable to ours as the patients selected had good prognosis factors (good general condition, good response to chemotherapy, weak extension of the disease).

In addition, the probability of selection bias in our ILNR population must be considered. Indeed, the histological proof rate of ILNR is low, only concerning 24% of patients treated. It has been shown that there are discrepancies between evaluation of disease imaging and the actual spread of the disease both in lymph nodes[24] and in the peritoneum[25,26], even though recent advances in PET-CT are considerable, with sensitivity, specificity, positive predictive value and negative predictive value of 98.3, 91.2, 96.8 and 93.9%, respectively[27]. In the study by Legge *et al.*[18] 21.5% of patients suspected to have ILNR had peritoneal dissemination which was discovered during surgery.

ILNR in EOC is a rare event that does not seem to be associated with a better prognosis in terms of OS when compared to ICR. This rather ill-defined entity appears as a form of slow-moving recurrence with subsequent transformation to a more aggressive form.

In our study, 5-years' OS after initial diagnosis of EOC was 53.7% in ILNR group with median survival of 62 months. 5-year OS after diagnosis of recurrence was 15.3% with a median survival of 39 months. These data are consistent with literature data that found median OS after recurrence of between 26 to over 60 months[13–20,28].

These results must be analyzed with caution because they only pertain to a small number of patients for each location. Confusion biases are also to be considered. The first is differences in the management of relapse. It may be thought that the use of surgical treatment (24% in all locations combined) may have involved different proportions of patients depending on the location of the recurrence. As the most important part of the prognosis of EOC is the tumour residue[8,9,29,30], several studies [14–16,19,20] have shown that secondary cytoreduction, if it provides for complete excision of the disease, significantly improves OS particularly in the ILNR. Especially since some studies are in favour of relative chemoresistance from metastatic LN locations in EOC[31,32]. The second is the possible lack of awareness of peritoneal involvement associated with various levels of severity between groups.

Repeat surgery for recurrent, platinum-sensitive ovarian cancer remains an open debate, as available studies reported disparate results. a large, randomized study (DESKTOP III) showed significant improvement in progression-free survival (PFS) with secondary surgical debulking.

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A retrospective analysis of a clinical registry from Norway showed a strong association between treatment-free interval, complete surgical resection, and both PFS and OS as compared with patients who received only chemotherapy at recurrence.

The Gynecologic Oncology Group (GOG 213) trial showed no survival benefit (PFS or OS) for patients who had secondary cytoreductive surgery, followed by chemotherapy, versus those who received chemotherapy alone. Median OS was a year longer for the nonsurgical group. In this trial, surgery achieved complete surgical resection in 68% of patients slightly less than the 72.5% in the desktop III trial.

Patient selection criteria for the DESKTOP III study consisted of >6-month platinum-free interval plus good performance status, no residual disease after primary surgery, and <500 mL of ascites. The GOG trial had no specific eligibility criteria for secondary surgery, stipulating only that the assessment should consist of a physical exam, appropriate laboratory tests, and imaging (MRI, PET/CT, or CT). The protocol did identify certain unfavourable characteristics: carcinomatosis, large-volume ascites, and parenchymal-organ involvement.

Complete surgical resection is consistently associated with better overall survival than residual disease but case selection remains challenging and controversial among many centers.

Finally, the proportion of complete lymphadenectomies performed was higher in the ILNR group. Routine lymphadenectomy means occult LN invasion cannot be missed[36–38]. The study by Morice *et al*.[37] found that in a population of 276 patients with systemic para-aortic and pelvic lymphadenectomy, LN involvement was present in 20% (17/85), 40% (6/15), and 55% (99/176) for FIGO stages I, II and III / IV respectively. Lymphadenectomy would appear to be an independent predictor of improved overall survival in EOC (56-57). Rouzier *et al*.[39] have also shown that the greater the number of lymph nodes examined, the better the prognosis. In their study, 5-year cause-specific survival was 37% for the group of patients where no lymph nodes were examined, 62% for the group with one to nine lymph nodes removed, and 71% for the group with more than ten lymph nodes had been examined (p <0.001). Among studies evaluating ILNR in EOC, the frequency of lymphadenectomy is low, ranging from 25 to 57%, including lymphadenectomy limited to the para aortic or pelvic region [13–20].

In a study including forty-nine isolated lymph node relapse ovarian carcinoma patients matched to 49 extranodal relapse cases using the Edinburgh Ovarian Cancer Database. [40]
Isolated lymph node relapse cases demonstrated significantly prolonged postrelapse survival and overall survival vs extranodal relapse upon multivariable analysis (HR^{multi} = 0.52 [0.33-0.84] and 0.51 [0.31-0.84]). Diagnostic specimens from high-grade serous ovarian carcinomas that subsequently displayed isolated lymph node relapse harbored significantly greater CD3+ and CD8+ cell infiltration compared to extranodal relapse cases (P = .001 and P = .009, Bonferroni-adjusted P = .003 and P = .019). Isolated lymph node relapse high-grade serous ovarian carcinoma cases did not show marked enrichment or depletion of cases with

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BRCA1/2 mutation or CCNE1 copy number gain when compared to their extranodal relapse counterparts (24.4% vs 19.4% and 18.2% vs 22.6%, P = .865 and P = .900).

This study has other several limitations. It was based on a retrospective database with heterogenous data entries from the different treatment centers. A substantial number of patients had missing data and some had to be excluded as a result. Also, Patients with ILNR were mainly treated with chemotherapy, whereas surgical effort could have been more offered. This may be a biais of the study and alter the prognosis of patients with ILNR

Conflict of author's statement
The authors declare that they have no conflict of interest

CONCLUSION

ILNR in EOC is a rare event that does not seem to be associated with a better prognosis in terms of OS when compared to ICR. This rather ill-defined entity appears as a form of slow-moving recurrence with subsequent transformation to a more aggressive form. The number of invaded pelvic LN during initial management of EOC seems to be a predictor of occurrence of ILNR.

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Figure legends

Figure 1: Overall Survival after initial diagnosis of ovarian cancer according to the type of recurrence.

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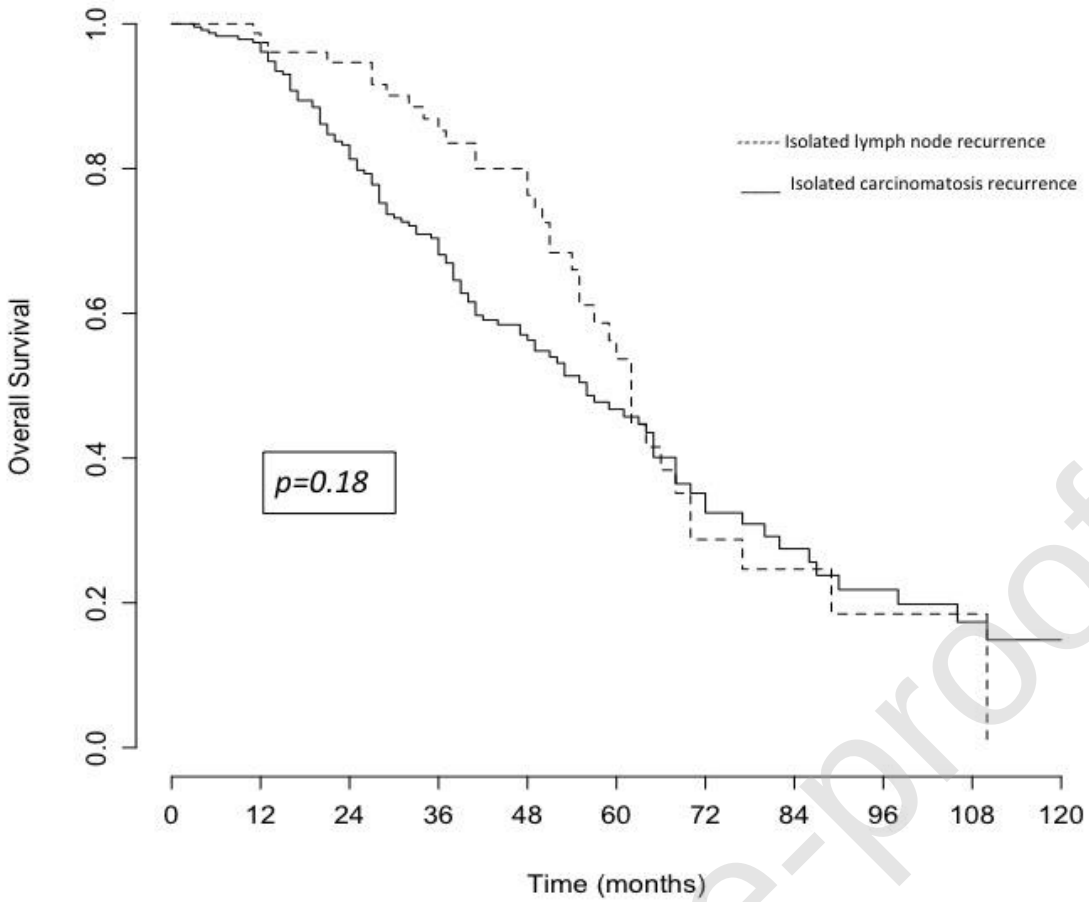
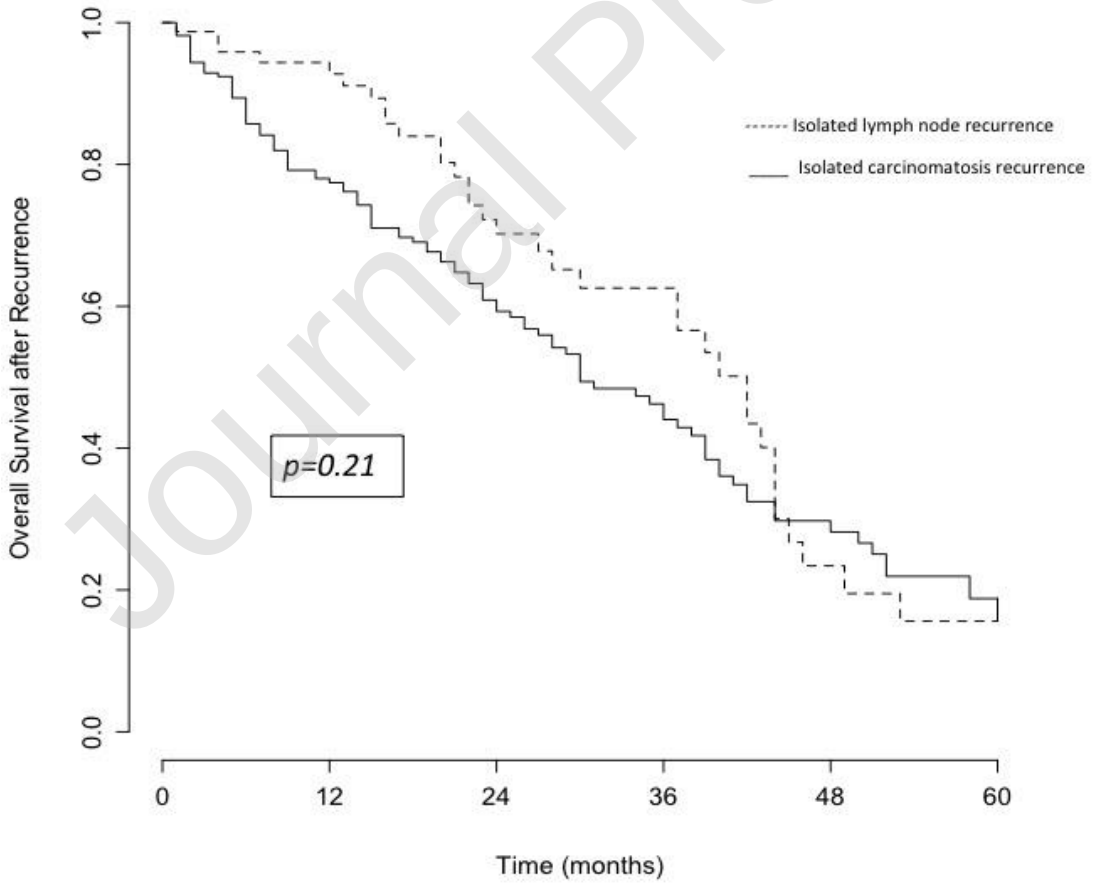


Figure 2: Overall Survival after first relapse according to the type of recurrence.



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