European Journal of Surgical Oncology 45 (2019) 376–382

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

The impact of radiological retroperitoneal lymphadenopathy on survival after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal peritoneal metastases

L.R. van der Werf [a], E. Wassenaar [b], A. de Niet [a], F. Lalezari [c], H.J. Braam [d], B. van Ramshorst [b], J. Nederend [e], I.H.J.T. de Hingh [d], N.F.M. Kok [a], A.G.J. Aalbers [a, *]

[a] Department of Surgical Oncology, The Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, the Netherlands
[b] Department of Surgical Oncology, Antonius Hospital, Nieuwegein, the Netherlands
[c] Department of Radiology, The Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, the Netherlands
[d] Department of Surgical Oncology, Catharina Hospital, Eindhoven, the Netherlands
[e] Department of Radiology, Catharina Hospital, Eindhoven, the Netherlands

ARTICLE INFO

Article history:
Received 5 July 2018
Received in revised form
10 October 2018
Accepted 28 October 2018
Available online 1 November 2018

Keywords:
Retroperitoneal lymphadenopathy
Hipec
peritoneal metastases
Retroperitoneal lymph nodes
CRS-HIPEC

ABSTRACT

Objectives: To investigate the impact of retroperitoneal lymphadenopathy (RPLP) on pre-operative CT scan on overall survival (OS) and disease-free survival (DFS) after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) for peritoneal metastases (PM) of colorectal cancer.
Background: In patients with PM enlarged retroperitoneal lymph nodes (RPLP) are usually considered *extra-regional lymph node* metastases and therefore these patients may be excluded from CRS-HIPEC. This is a clinical dilemma since it is often hard to obtain histology from these nodes.
Methods: In this multicenter, retrospective study all consecutive patients with colorectal PM treated with CRS-HIPEC between 2004 and 2013 were included. The preoperative CT-scan was re-analyzed for the presence of RPLP based on the radiological appearance of enlarged lymph nodes. Outcomes were OS and DFS. Kaplan-Meier methods and Cox regression modeling were used to analyze the impact of RPLP on OS and DFS.
Results: In 25 of 401 patients (6.1%) RPLP was observed on the preoperative CT-scan. Patient, tumor and surgical characteristics did not statistically significantly differ between groups with and without RPLP. After a median follow-up of 46 months, the one-, three- and five-year survival was 80%, 59%, 38% and 90%, 50%, 36% in the group with and without RPLP respectively. Median OS (47 vs. 35 months, logrank: $p = 0.70$) and median DFS (14 vs. 15 months, logrank: $p = 0.81$) did not statistically significantly differ between groups. In multivariable analysis, RPLP did not significantly influence survival.
Conclusion: Enlarged retroperitoneal lymph nodes on a pre-operative CT-scan should not automatically exclude patients from CRS-HIPEC.

Introduction

Colorectal cancer (CRC) is common and among the leading causes of cancer-related death [1]. Peritoneal metastases (PM) occur in approximately 5% of patients with CRC [2]. Without adequate treatment, median survival of patients with colorectal PM is approximately 6 months [3]. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) is a potential curative treatment for PM [4–6]. A median survival up to 48 months has been reported depending on patient selection [7]. Nodal stage of the primary tumor (N-stage), extent of PM, histology of the primary tumor and completeness of cytoreductive surgery are the most important prognostic factors for disease-free and overall survival [8,9].

CRS-HIPEC may cause major morbidity including

* Corresponding author. The Netherlands Cancer Institute – Antoni van Leeuwenhoek, Department of Surgical Oncology, POBOX 90203, 1006 BE Amsterdam the Netherlands.
E-mail addresses: l.r.vdwerf@gmail.com (L.R. van der Werf), a.aalbers@nki.nl (A.G.J. Aalbers).

https://doi.org/10.1016/j.ejso.2018.10.540
0748-7983/

enterocutaneous fistula and anastomotic leakage) and have significantly impact on quality of life up to six months post-operative [10,11]. Patients with associated systemic metastases are usually excluded from CRS-HIPEC because of poor anticipated survival.

Enlarged retroperitoneal lymph nodes are frequently considered *extra-regional lymph node* metastases and like patients with *distant* metastases are usually excluded from CRS-HIPEC. Enlarged retroperitoneal lymph nodes discovered during preoperative radiological staging may either host *extra-regional lymph node* metastases or be enlarged because of an immunological or inflammatory response to tumor or infection. Accurate diagnosis of the nature of the retroperitoneal lymphadenopathy is difficult. Most often a CT-scan or PET-scan is used to diagnose retroperitoneal lymphadenopathy (RPLP) as access for biopsy is difficult. Because these difficulties in the diagnosis of RPLP, critical evaluation of the outcomes of patients with RPLP is needed. The aim of this multicenter retrospective study was to address the impact of RPLP as diagnosed on pre-operative imaging on survival in patients who underwent CRS-HIPEC.

Methods

This was a multicenter retrospective observational cohort study, including patients of three Dutch tertiary referral centers. In these centers, similar protocols and inclusion criteria for CRS-HIPEC have been used [12]. All patients who underwent CRS-HIPEC between 2004 and 2013 were eligible for this study if they had undergone CRS-HIPEC for PM of CRC including true appendix carcinomas infiltrating the caecum or other way around. Exclusion criteria included synchronous liver metastases, absence of a CT-scan performed within 1 month prior to the operation, extensive residual disease after cytoreduction (>2.5 mm nodules, Completeness of Cytoreduction Score CC-2) or neoplasms of the appendix including low grade and high grade mucinous neoplasms. Retroperitoneal lymphadenectomies were not performed for enlarged retroperitoneal nodes. The study was carried out in accordance with the Helsinki Declaration of 1964 and later versions. The medical ethical committee was consulted and they concluded that according to the Dutch law on Medical Research in Humans and given the retrospective design, the current study did not require informed consent by involved patients. According to Good Clinical Practice, all patient derived data were anonymized.

Data collection

Data were retrieved from prospectively developed institutional databases. For all patients, the pre-operative CT-scan was re-analyzed by a trained researcher together with a radiologist experienced in the assessment of patients with peritoneal metastases to screen for the presence of retroperitoneal lymphadenopathy. Retroperitoneal lymph nodes were considered enlarged if the short axis was larger than normal as described by Vinnicome et al. and Dorfman et al. [13,14]. These values included for para-aortic and caval nodes (high): ≤9 mm, para-aortic and caval nodes (lower): ≤11 mm, common iliac nodes: ≤ 9 mm, internal iliac nodes: ≤7 mm, external iliac nodes: ≤10 mm.

Patient characteristics, tumor characteristics and treatment characteristics were recorded including demographics and variables of the primary tumor such as TNM-status, differentiation grade and synchronous or metachronous occurrence of PM. Systemic chemotherapy was subdivided in neoadjuvant, adjuvant, or no chemotherapy. Standard treatment consistent of CRS-HIPEC and adjuvant fluoropyrimidin based treatment. Neoadjuvant chemotherapy has never been the standard of care in the Netherlands, but was considered in some patients if they. had undergone laparotomy a few weeks earlier or if they had signs of distant metastases or extra-regional lymph node metastases (such as retroperitoneal lymphadenopathy). In the participating hospitals, a simplified version of the Peritoneal Cancer Index (PCI) was used to describe the extend of PM [15]. In this score, the abdomen was divided in seven regions and the presence of PM was recorded. The number of regions were grouped because of the small number of patients in the RPLP group: zero to two, three to five and six or seven. Completeness of cytoreduction was graded as no residual disease, residual nodules smaller than 2.5 mm and nodules larger than 2.5 mm. Intentionally, cytoreduction was only performed if the surgeon expected to achieve complete cytoreduction. In general, PM in more than 5 regions and expected R2 resection were considered contra-indications for CRS-HIPEC [5]. Information of pathological analysis of lymph nodes and radiological follow-up was recorded whenever available. The main outcome of the study was overall survival (OS). The secondary outcome was disease-free survival (DFS).

Statistical analysis

Baseline characteristics were compared between treatment groups using Fisher exact test, Pearson χ^2 or Mann Whitney *U* test as appropriate. Continuous variables were tested using Mann-Whitney U tests. DFS and OS were assessed using the Kaplan-Meier method. The influence of clinically relevant factors on DFS and OS was investigated using multivariable Cox regression analysis. The factors tested included subtype (mucinous/not mucinous), differentiation grade, location, T-, N–, M – stage of the primary tumor, synchronous/metachronous PM, number of regions affected, completeness of cytoreduction score, and systemic chemotherapy. These factors were first studied in univariable models using Log Rank tests and if considered clinically relevant (i.e. retroperitoneal lymph node status) or a p-value <0.10 was observed, the factor was included in the multivariable model. For all other tests a p-value <0.05 was considered statistically significant. Statistical Package for the Social Sciences® (SPSS) version 20 (IBM) was used for the statistical analysis.

Results

401 patients were eligible for analysis (Fig. 1). The median follow-up was 45.0 months [interquartile range (IQR) 28.5–64.0]. On the preoperative CT-scan RPLP was observed in 25 patients (6.2%). In 18 of the 25 patients (72%), the RPLP was already described in the initial report. The specific location of pathological lymph nodes is shown in Table 1. Seven patients had RPLP in more than one region.

Patient-, disease-, and treatment characteristics

Patient- and disease characteristics were not significantly different between the RPLP and control group. Patients with RPLP were significantly more often treated with systemic chemotherapy ($p = 0.003$). 14 of 25 (56%) RPLP patients were treated with neoadjuvant chemotherapy, 11 of 25 (44%) with adjuvant chemotherapy, and 4 of 25 patients (16%) were neither treated with neoadjuvant and adjuvant chemotherapy. Other treatment characteristics were not significantly different between groups (Table 2).

RPLP patients

In Fig. 2, the diagnostics and follow-up process of the patients

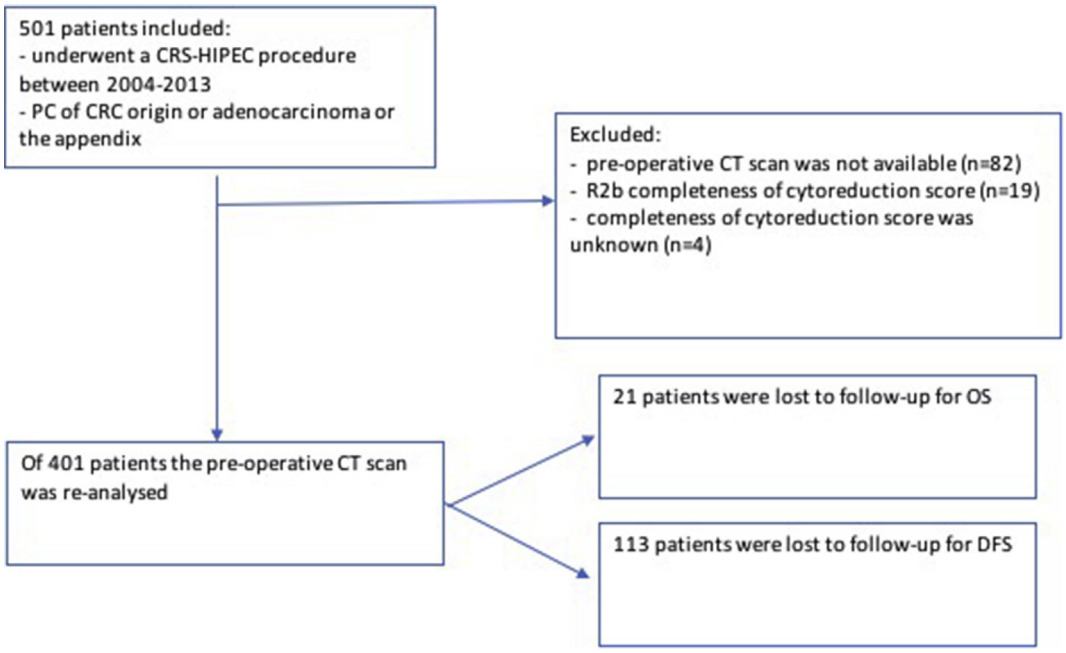

Fig. 1. Flowchart inclusion (CRS-HIPEC: cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, PC: Peritonitis Carcinomatosa, CRC: colorectal carcinoma, CT: computotomography, OS: overall survival, DFS: disease-free survival)

Table 1
RPLP characteristics of the patient cohort.

Patient cohort	n = 401
No RPLP	376 (93.8%)
RPLP	25 (6.2%)
Paracaval	5
Paraaortic	11
Parailiac (common)	7
Parailiac (external)	3
Parailiac (internal)	3

with RPLP is shown. In 11 patients, at least one of the retroperitoneal lymph nodes were PET-positive or tumor cells were observed at pathological examination of retroperitoneal lymph nodes. In the remaining 14 patients, the nature of the RPLP could not be confirmed because of various reasons, including 7 patients in whom enlarged retroperitoneal nodes were not noted preoperatively. Eight (57%) of these 14 patients were treated with chemotherapy before CRS-HIPEC (neoadjuvant or adjuvant for the primary tumor). There were no significant differences between the groups with and without pathological proven RPLN metastasis and/or PET positive LNs (supplementary Table 1).

Survival

After a median follow-up of 60 months [IQR 54–73] 9 patients from the RPLP group (32%) were alive of whom 6 (25%) with no evidence of disease. After a median follow up of 56 months [IQR 39–83] 141 (34%) patients were alive in the control group and 87 (21%) of them did not have signs of recurrence. Twenty-one patients were lost to follow-up and censored. Kaplan-Meier curves for OS an DFS for patient with and without RPLP are shown in Fig. 3a and b. The overall survival and disease-free survival were not statistically significant different ($p = 0.58$ and $p = 0.24$ respectively). The one-, three- and five-year survival was respectively 80%, 59% and 38% in the group with RPLP and 90%, 50% and 36% in the control group. Median overall survival and disease-free survival in the RPLP group was 47 and 14 months, compared to 35 and 15 months in the control group, respectively. Survival curves for patients with RPLP with ($n = 11$), and without ($n = 14$) pathological or PET proven positive lymph nodes are shown in the supplementary Fig. 1a and 1b.

Multivariable analysis of OS

Variables which significantly influenced OS in univariable analysis included sex, differentiation grade, location and N-stage of the primary tumor, the number of affected regions, completeness of cytoreduction and systemic chemotherapy. In univariable analysis RPLP was not significantly associated with OS. All significant variables were added to the multivariable model together with RPLP. The multivariable model showed that sex, N-status of the primary tumor, number of affected regions, CCS score and systemic chemotherapy significantly influenced OS (Table 3). The multivariable model did not show influence of RPLP on OS.

Multivariable analysis of DFS

Variables which significantly influenced DFS in univariable analysis included differentiation grade, location and N-stage of the primary tumor, the number of affected regions, completeness of cytoreduction, and systemic chemotherapy. In univariable analysis RPLP was not significantly associated with DFS. All significant variables were added to the multivariable model together with RPLP. The multivariable model showed that differentiation, location and N-status of the primary tumor, number of affected regions, CCS score and systemic chemotherapy had significant influence on DFS (Table 3). RPLP was not associated with DFS.

Discussion

This study shows that RPLP observed on a pre-operative CT-scan is not associated with decreased OS or DFS as compared to patients without RPLP. Selection of patients is the key to success in the

Table 2
Clinicopathological and treatment characteristics of the patient cohort in RPLN positive and RPLN negative patients. Data are median with IQR or n (%).

Demographical characteristics	RPLP+ (n = 25)	RPLP- (n = 376)	p value
Men	11 (44%)	175 (54%)	0.8
Age at CRS-HIPEC, years (median [IQR])	55 [49–60]	59 [52–65]	0.07
Primary tumor characteristics			
Tumor subtype			0.39
Nonmucinous adenocarcinoma	20 (80%)	271 (72%)	
Mucinous adenocarcinoma	5 (20%)	105 (28%)	
Tumor differentiation			0.19
Good	0 (0.0%)	18 (4.8%)	
Moderate	17 (68%)	175 (47%)	
Poor	4 (16%)	48 (13%)	
Signet cell	2 (8.0%)	27 (7.2%)	
Unknown	2 (8.0%)	108 (29%)	
Primary tumor location			0.67
Rectum	5 (20%)	64 (17%)	
Colon	18 (72%)	279 (74%)	
Appendix (adenocarcinoma)	2 (8.0%)	26 (6.9%)	
Missing	*0 (0.0%)*	*7 (1.7%)*	
T-status primary tumor			0.89
T0-T2	1 (4.0%)	14 (3.7%)	
T3	12 (48%)	152 (40%)	
T4	11 (44%)	190 (51%)	
Tx	1 (4.0%)	20 (5.3%)	
N-status primary tumor			0.76
N0	5 (20%)	111 (30%)	
N1	8 (32%)	109 (29%)	
N2	11 (44%)	138 (37%)	
Nx	1 (4.0%)	18 (4.8%)	
M-status at diagnosis of primary tumor			0.71
M0	10 (40%)	121 (32%)	
M+	14 (56%)	241 (64%)	
Mx	1 (4.0%)	14 (3.7%)	
PM and treatment characteristics			
PM			0.55
Synchronous	15 (60%)	212 (56%)	
Metachronous	10 (40%)	147 (39%)	
Missing	*0 (0.0%)*	*17 (4.5%)*	
Number of regions affected			0.66
0–2 regions	13 (52%)	157 (42%)	
3–5 regions	11 (48%)	184 (49%)	
6–7 regions	1 (4.0%)	25 (6.6%)	
Missing	*0 (0.0%)*	*10 (2.7%)*	
Completeness of cytoreduction score (CCS)			0.52
Complete resection (R0 and R1)	24 (96%)	348 (93%)	
Incomplete resection (R2a)	1 (4.0%)	28 (7.4%)	
Systemic chemotherapy			0.003
Yes	21 (84%)	143 (38%)	
No	4 (16%)	185 (49%)	
Unknown	0 (0.0%)	48 (13%)	

surgical treatment of peritoneal metastases. The presence of RPLP raised the suspicion of lymph node metastasis. Patients with *distant* metastases of CRC are usually excluded from CRS-HIPEC. Balancing between treatment related morbidity and mortality and potential survival benefit is essential. It is a clinical dilemma to deny patients a potentially curative treatment because of clinically suspicious but not pathologically confirmed RPLP. The current study reveals that the presence of RPLP on pre-operative staging does not influence OS and DFS. Apparently other factors including N-stage of the primary tumor, extent of peritoneal metastases and completeness of surgical cytoreduction have effect on survival. These factors are consistent prognostic factors throughout the literature [16].

For retroperitoneal lymph node metastases of CRC, with no presence of PM, the current literature suggests that a more aggressive surgical treatment might be associated with improved survival [17]. Gagnière et al. showed relatively limited morbidity and median overall survival of 60 months and DFS of 14 months in patients with retroperitoneal lymph node metastases who underwent radical retroperitoneal lymphadenectomy [18].

Little is known of patients with PM and RPLP who have been treated with CRS-HIPEC. Though the absolute number of patients with enlarged nodes is small, the total number of patients in this study is large. This shows that patients with radiologically enlarged retroperitoneal lymph nodes are uncommon in cohorts of patients who underwent CRS-HIPEC. Data of a substantial number of patients and their imaging has been reviewed to collect data of what still is a small sample. Therefore this study which reports the outcomes of patients with RPLP is unique. For other *distant* metastases, in particular liver metastases, there is evidence that these patients may benefit from CRS-HIPEC [19]. A 5-year survival of 38.5% is reported for patients with liver metastases and PM who underwent CRS-HIPEC [20]. In the current study, comparable 5-year survival (38%) and median OS (47 months) is shown for the RPLP group. Therefore, we advocate that also selected patients with RPLP may benefit from CRS-HIPEC.

Since no pathological examination was performed in 18 of the

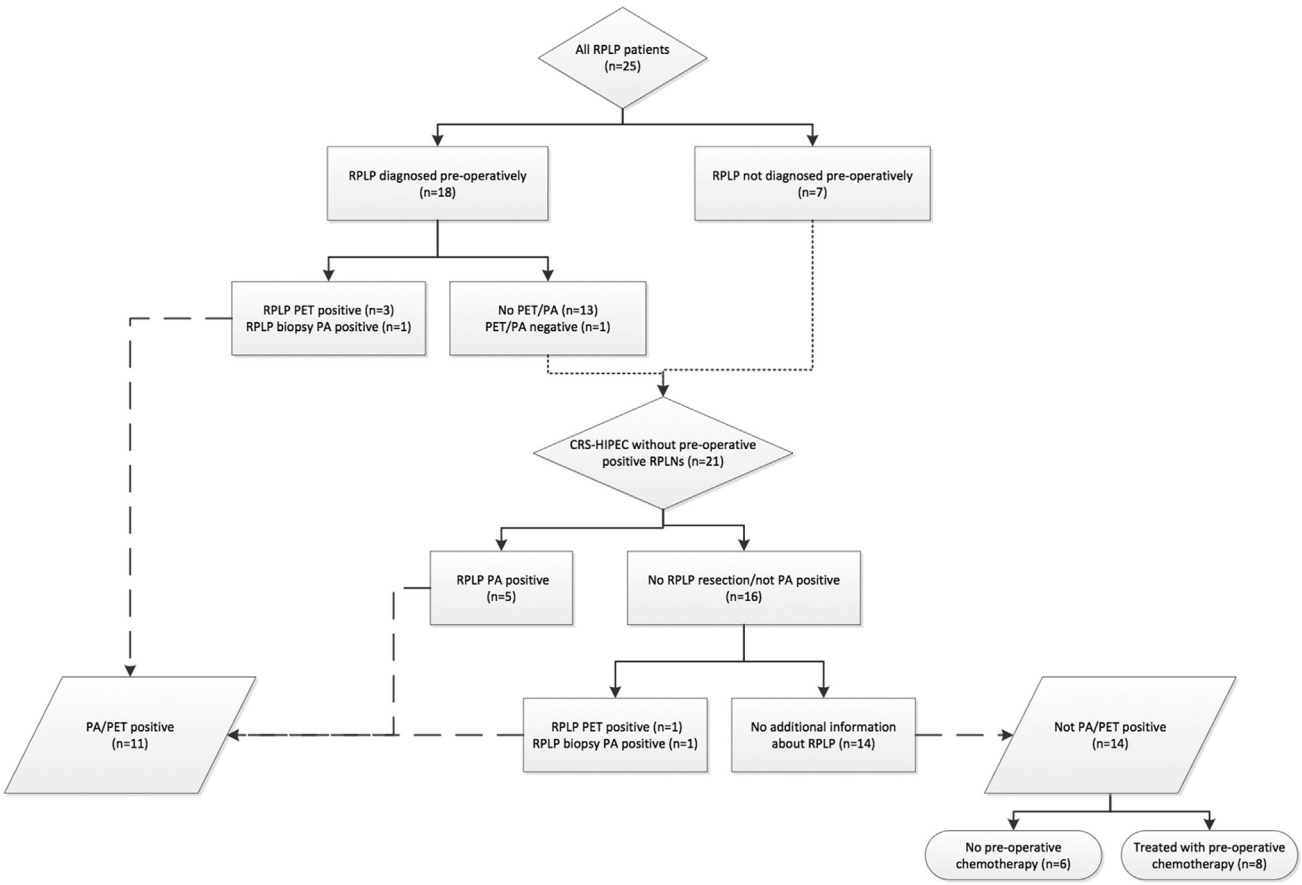

Fig. 2. Overview diagnostic process RPLP (RPLP: retroperitoneal lymphadenopathy, PET: positron emission tomography, PA: pathological assessment)

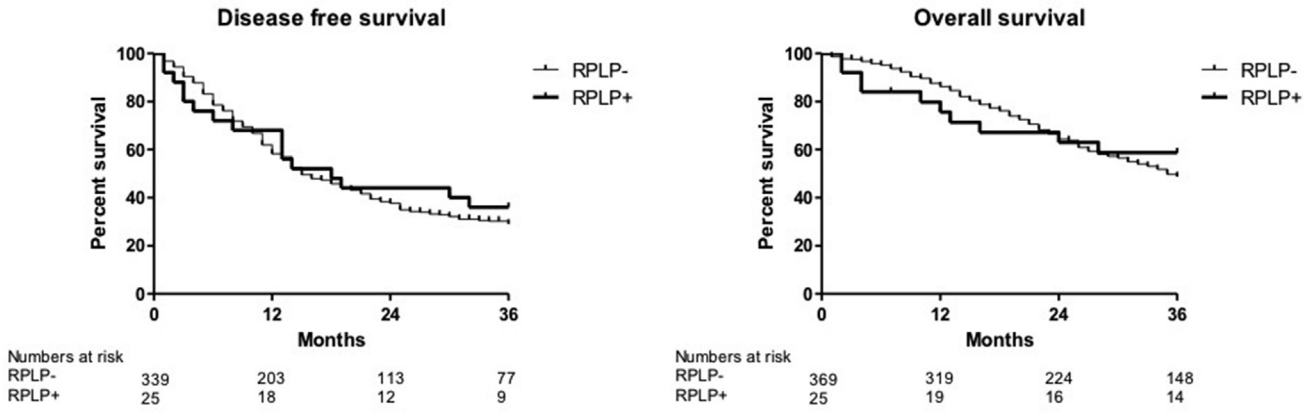

Fig. 3. Overall and disease free survival curves for RPLP+ versus RPLP- (RPLP: retroperitoneal lymphadenopathy)

25 patients, the RPLP on CT-scan may be caused by an immunological or inflammatory response to tumor or infection instead of metastases. It would have been valuable if radiological suspected lymph nodes had been proven malignant by detecting tumor cells or signs of tumor regression in pathological examination. The presence of enlarged nodes on pre-operative imaging, without pathological confirmation of metastasis, leads to a heterogeneous group which consequently influences outcomes. However, even in the patients whose nodes were sampled for pathological analysis, presence of metastases did not always exclude long-term survival. Underreporting of retroperitoneal lymph node metastasis in this study may also have been possible in this study, as retroperitoneal nodes have not been pathologically investigated in all 401 patients. This is a major limitation of the study We acknowledge that the RPLP patients in this study were significantly more often treated with systemic chemotherapy and the majority of RPLP patients was treated with neoadjuvant chemotherapy. As the absolute number is low, neither multivariable analysis patient-matched propensity scored analysis will correct for these differences between groups and therefore the results have to be viewed with caution.

Other limitations of this study include selection bias and a small group size. Only patients who underwent CRS-HIPEC were included

Table 3
Results of uni- and multivariable Cox proportional hazard model for OS and DFS.

Subgroups	Univariable analysis				Multivariable analysis			
	OS		DFS		OS		DFS	
	Hazard ratios [95% CI]	*p value*	*Hazard ratios [95% CI]*	*p value*	*Hazard ratios [95% CI]*	*p value*	*Hazard ratios [95% CI]*	*p value*
Retroperitoneal lymphadenopathy		0.56		0.64				0.96
Without RPLP	1		1		1	0.71	1	
With RPLP	0.86 [0.51–1.45]		0.89 [0.55–1.46]		1.11 [0.64–1.92]		0.99 [0.59–1.65]	
Sex		0.01		0.42		0.007		
Men	1		1		1			
Women	0.72 [0.56–0.93]		0.90 [0.70–1.16]		0.69 [0.53–0.90]			
Age (in years)		0.43		0.24				
<70	1		1					
≥70	1.17 [0.80–1.70]		0.79 [0.53–1.17]					
Tumor subtype		0.44		0.88				
No mucinous adenocarcinoma	1		1					
Mucinous adenocarcinoma	1.11 [0.85–1.47]		1.02 [0.77–1.35]					
Tumor differentiation		0.04		0.02		0.53		0.008
Good	1		1		1		1	
Moderate	1.56 [0.81–2.98]	0.18	1.40 [0.76–2.60]	0.28	1.95 [1.00–3.79]	0.05	1.48 [0.79–2.78]	0.22
Poor	1.51 [0.73–3.11]	0.27	1.11 [0.56–2.23]	0.76	1.98 [0.94–4.17]	0.07	1.17 [0.58–2.37]	0.65
Signet cell	2.98 [1.41–6.32]	0.004	2.70 [1.30–5.60]	0.008	3.23 [1.48–7.05]	0.003	3.07 [1.43–6.62]	0.004
Unknown	1.50 [0.77–2.91]	0.24	1.31 [0.68–2.48]	0.41	2.22 [1.23–4.38]	0.02	1.87 [0.97–3.61]	0.06
Tumor location		0.08		0.02		0.14		0.05
Colon	1		1		1		1	
Appendix (adenocarcinoma)	0.43 [0.23–0.82]	0.01	0.46 [0.25–0.84]	0.01	2.14 [1.08–4.25]	0.03	2.25 [1.15–4.40]	0.02
Rectum	1.03 [0.74–1.44]	0.85	1.14 [0.83–1.56]	0.43	2.27 [1.08–4.81]	0.03	2.78 [1.34–5.80]	0.006
Missing	0.87 [0.32–2.33]	0.76	0.21 [0.03–1.52]	0.12	1.00 [0.17–6.00]	0.99	1.00 [0.06–15.66]	0.99
T-status primary tumor		0.88		0.60				
T0-T2	1		1					
T3	1.27 [0.62–2.60]	0.52	1.01 [0.53–1.93]	0.98				
T4	1.18 [0.58–2.42]	0.65	0.99 [0.52–1.88]	0.97				
Tx	1.11 [0.48–2.76]	0.82	0.65 [0.27–1.55]	0.33				
N-status primary tumor		<0.001		<0.001		0.006		0.02
N0	1		1		1		1	
N1	2.00 [1.40–2.83]	<0.001	1.84 [1.31–2.56]	<0.001	1.70 [1.18–2.47]	0.005	1.64 [1.15–2.33]	0.007
N2	2.16 [1.55–3.03]	<0.001	1.88 [1.37–2.59]	<0.001	1.89 [1.31–2.73]	0.001	1.72 [1.21–2.45]	0.003
Nx	1.19 [0.61–2.35]	0.40	0.78 [0.43–1.88]	0.78	1.59 [0.68–3.70]	0.28	1.37 [0.60–3.09]	0.45
M-status at diagnosis of primary tumor		0.23		0.36				
M0	1		1					
M+	1.27 [0.96–1.67]	0.07	1.12 [0.86–1.46]	0.34				
Mx	1.02 [0.51–2.04]	0.68	0.35 [0.29–1.54]	0.35				
PC		0.72		0.64				
Synchronous	1		1					
Metachronous	0.92 [0.71–1.20]	0.48	1.00 [0.78–1.29]	0.94				
Missing	1.14 [0.61–2.10]	0.72	0.70 [0.33–1.49]	0.31				
Number of regions affected		<0.001		0.001		<0.001		0.001
0–2 regions	1		1		1		1	
3–5 regions	1.93 [1.46–2.55]	<0.001	1.42 [1.09–1.84]	0.009	2.28 [1.71–3.05]	<0.001	1.58 [1.21–2.07]	0.001
6–7 regions	3.12 [1.90–5.10]	<0.001	2.29 [1.40–3.73]	0.001	2.73 [1.60–4.68]	<0.001	2.31 [1.38–3.89]	0.002
Missing	1.71 0.74–3.92]	0.08	0.23 [0.03–1.70]	0.15	3.58 [0.92–13.93]	0.07	1.36 [0.60–3.09]	0.55
Completeness of cytoreduction score (CCS)		0.003		0.14		0.09		0.89
Complete resection (R0 and R1)	1		1		1		1	
Incomplete resection (R2a)	1.90 [1.24–2.93]		1.41 [0.89–2.22]		1.47 [0.94–2.30]		0.97 [0.60–1.56]	
Systemic chemotherapy		<0.001		0.002		<0.001		0.001
No	1		1		1		1	
Yes	0.50 [0.37–0.64]	<0.001	0.62 [0.48–0.81]	<0.001	0.41 [0.31–0.55]	<0.001	0.59 [0.45–0.78]	<0.001
Unknown	0.54 [0.35–0.82]	0.002	0.68 [0.44–1.03]	0.07	0.45 [0.27–0.75]	0.002	0.67 [0.41–1.10]	0.11
Time*retroperitoneal nodes	1.03 [0.97–1.09]	0.32	1.01 [0.95–1.07]	0.70				

in this study. Patients who were not referred or who were excluded from CRS-HIPEC because of too extensive disease have not been included. The sample size of the RPLP group is low but currently highest compared to the existing literature.

In conclusion, this retrospective multicenter study showed that radiological retroperitoneal lymphadenopathy is uncommon in patients undergoing CRS-HIPEC. RPLP was not correlated with significantly decreased OS or DFS in patients treated with CRS-HIPEC. Therefore, RPLP diagnosed on a pre-operative CT-scan should not be regarded as a contra-indication for CRS-HIPEC. In our opinion the clinical value of this study is that radiologically suspicious nodes do not necessary preclude surgical treatment in these patients. In patients were RPLP is seen on a preoperative CT-scan, an additional PET-scan could help to determine the nature of RPLP. In case the retroperitoneal lymph nodes are PET-positive, induction chemotherapy could be considered instead of upfront exclusion for CRS-HIPEC. Pathological examination of resected retroperitoneal lymph nodes during CRS-HIPEC should be performed to unravel the real consequences of pathological RPLP on survival.

Funding

None declared.

Disclosures

The authors have declared no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejso.2018.10.540.

References

[1] National Cancer Registry TN.
[2] Lemmens VE, Klaver YL, Verwaal VJ, et al. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. Int J Canc 2011;128:2717–25.
[3] Sadeghi B, Arvieux C, Glehen O, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer 2000;88:358–63.
[4] Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003;21:3737–43.
[5] Verwaal VJ, Bruin S, Boot H, et al. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol 2008;15:2426–32.
[6] Kuijpers AM, Mirck B, Aalbers AG, et al. Cytoreduction and HIPEC in The Netherlands: nationwide long-term outcome following the Dutch protocol. Ann Surg Oncol 2013;20:4224–30.
[7] Elias D, Mariani A, Cloutier AS, et al. Modified selection criteria for complete cytoreductive surgery plus HIPEC based on peritoneal cancer index and small bowel involvement for peritoneal carcinomatosis of colorectal origin. Eur J Surg Oncol 2014;40:1467–73.
[8] van Oudheusden TR, Braam HJ, Nienhuijs SW, et al. Poor outcome after cytoreductive surgery and HIPEC for colorectal peritoneal carcinomatosis with signet ring cell histology. J Surg Oncol 2015;111:237–42.
[9] van Eden WJ, Kok NF, Jozwiak K, et al. Timing of systemic chemotherapy in patients with colorectal peritoneal carcinomatosis treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Dis Colon Rectum 2017;60:477–87.
[10] Dodson RM, McQuellon RP, Mogal HD, et al. Quality-of-Life evaluation after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol 2016;23:772–83.
[11] Kusamura S, Younan R, Baratti D, et al. Cytoreductive surgery followed by intraperitoneal hyperthermic perfusion. Cancer 2006;106:1144–53.
[12] Kuijpers AMJ, Aalbers AGJ, Nienhuijs SW, et al. Implementation of a standardized HIPEC protocol improves outcome for peritoneal malignancy. World J Surg 2015;39:453–60.
[13] Vinnicombe SJ, Norman AR, Nicolson V, Husband JE. Normal pelvic lymph nodes: evaluation with CT after bipedal lymphangiography. Radiology 1995;194:349–55.
[14] Dorfman RE, Alpern MB, Gross BH, Sandler MA. Upper abdominal lymph nodes: criteria for normal size determined with CT. Radiology 1991;180:319–22.
[15] Verwaal VJ, van Tinteren H, van Ruth S, Zoetmulder FA. Predicting the survival of patients with peritoneal carcinomatosis of colorectal origin treated by aggressive cytoreduction and hyperthermic intraperitoneal chemotherapy. Br J Surg 2004;91:739–46.
[16] Simkens GA, van Oudheusden TR, Nieboer D, et al. Development of a prognostic nomogram for patients with peritoneally metastasized colorectal cancer treated with cytoreductive surgery and HIPEC. Ann Surg Oncol 2016;23:4214–21.
[17] Ho TW, Mack LA, Temple WJ. Operative salvage for retroperitoneal nodal recurrence in colorectal cancer: a systematic review. Ann Surg Oncol 2011;18:697–703.
[18] Gagniere J, Dupre A, Chabaud S, et al. Retroperitoneal nodal metastases from colorectal cancer: curable metastases with radical retroperitoneal lymphadenectomy in selected patients. Eur J Surg Oncol 2015;41:731–7.
[19] de Cuba EM, Kwakman R, Knol DL, et al. Cytoreductive surgery and HIPEC for peritoneal metastases combined with curative treatment of colorectal liver metastases: systematic review of all literature and meta-analysis of observational studies. Cancer Treat Rev 2013;39:321–7.
[20] Elias D, Faron M, Goere D, et al. A simple tumor load-based nomogram for surgery in patients with colorectal liver and peritoneal metastases. Ann Surg Oncol 2014;21:2052–8.