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1 **Title:** Prognostic Impact of Celiac Lymph Node Involvement in patients after Frontline
2 Treatment for Advanced Ovarian Cancer

3

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27

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29

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44

45 **Abstract**

46 **Introduction**

47 Completeness of cytoreduction is the most important prognostic factor in patients with
48 advanced ovarian cancer (OC). Extensive upper abdominal surgery has allowed to increase
49 the rate complete cytoreduction and the feasibility of resection of celiac lymph nodes (CLN)
50 and porta hepatis disease in these patients has been demonstrated. The aim of our study was to
51 assess the prognostic impact of CLN involvement in patients with primary advanced OC
52 undergoing a complete cytoreductive surgery (CRS).

53 **Material and methods**

54 We designed a retrospective unicentric study. We reviewed data from patients who underwent
55 CLN resection with or without porta hepatis disease resection, within upfront or interval
56 complete CRS in the frontline treatment of advanced epithelial OC between January 2008 and
57 December 2015. Patients were classified in two groups according to CLN status. Univariate
58 and multivariate analyses were conducted. Survival rates were estimated using Kaplan-Meier
59 method.

60 **Results**

61 Forty-three patients were included and positive CLN were found in 39.5% of them. The
62 median disease-free survival in the group of patients with positive and negative CLN were
63 11.3 months and 25.8 months, respectively. In multivariable analysis, both CLN involvement
64 and high peritoneal cancer index were independently associated with decreased disease-free
65 survival. Computed tomography re-reading by an expert radiologist has good sensitivity for
66 detection of positive CLN.

67 **Conclusion**

68 CLN involvement and high preoperative tumor burden are independently associated with
69 decreased survival after complete cytoreduction for OC. CLN involvement is a marker of

70 diffuse disease and an independent risk factor for early recurrent disease.

71

72 **Keywords:** celiac lymph node status, porta hepatis disease, advanced epithelial ovarian

73 cancer, peritoneal ovarian carcinomatosis, upper abdominal procedures.

74 **Text**

75 **1. INTRODUCTION**

76

77 Completeness of cytoreduction has demonstrated to have a more significant influence on
78 survival of patients with advanced ovarian cancer (OC) than the extent of the metastatic
79 disease present before the surgery[1]. In the last decades, there has been an evolution in the
80 surgical approach of advanced OC. The incorporation of extensive upper abdominal
81 procedures (UAP) has allowed to almost double the rate of optimal cytoreduction[2,3]. Celiac
82 lymph nodes (CLN) and porta hepatis (PH) are one of the disease sites, which can hinder a
83 complete cytoreduction. In order to improve complete cytoreduction rates, we demonstrated
84 the feasibility with an acceptable morbidity of the resection of CLN and PH disease in
85 patients with advanced or recurrent OC[4]. Moreover, we showed that disease in CLN in
86 primary or recurrent OC was a marker of disease severity and that these patients had a worse
87 oncologic outcome[5].

88 The aim of our study was to evaluate the prognostic impact of CLN involvement in a
89 homogeneous cohort of patients who underwent a complete cytoreductive surgery (CRS) for a
90 primary diagnosis of advanced OC (FIGO stage IIIC-IV).

91

92 **2. MATERIALS AND METHODS**

93

94 *2.1. Patients and study design*

95 A computer-generated search of our institution patient database was carried out to
96 retrospectively identify all patients who underwent CLN resection with or without PH disease
97 resection, within upfront or interval complete CRS in the frontline treatment of advanced
98 (FIGO stage IIIC-IV) epithelial ovarian, fallopian or primary peritoneal cancer between

99 January 2008 and December 2015 at the French Comprehensive Cancer Center, Institut
100 Claudius Regaud – Institut Universitaire du Cancer de Toulouse, France. Institutional Review
101 Board approval was obtained from our center.

102

103 *2.2.Preoperative assessment, surgery principles and chemotherapy treatment*

104 All the patients underwent a preoperative imaging study including a computed tomography
105 (CT) of the chest, abdomen and pelvis. In selected cases of extra-abdominal disease suspicion,
106 a positron emission tomography was performed.

107 All the surgical procedures were performed by two experienced oncological surgeons. The
108 surgical technique of CRS was performed following Sargarbaker principles of
109 peritonectomy[6] and the CLN and PH disease resection was carried out as we previously
110 described[4]. The extent and distribution of the disease throughout the 13 abdominopelvic
111 regions were evaluated with the peritoneal cancer index (PCI). The main goal of the surgery
112 was to obtain a complete cytoreduction, evaluated using the Completeness Cytoreduction
113 score[7]. The indication of CLN or PH disease resection was based on the intraoperative
114 findings of suspicious lymph nodes (those measuring more than 1 cm and/or indurated at
115 palpation) or carcinomatosis in the PH peritoneum, respectively. We used Aletti Score to
116 quantify the surgical complexity [8] and we evaluated postoperative complications following
117 Clavien-Dindo Classification [9].

118 The indication of neoadjuvant chemotherapy was based on the sum of procedures required to
119 achieve complete cytoreduction, on medical comorbidities, and on the potential to tolerate an
120 extensive procedure. Patients with deep infiltration of the small bowel mesentery, diffuse
121 carcinomatosis involving large parts of the small bowel, stomach, infiltration of the
122 duodenum or pancreas (not limited to the pancreatic tail), or more than two bowel resections
123 required to eradicate the disease were considered for neoadjuvant chemotherapy. After three

124 cycles of platinum and taxane-based chemotherapy, a clinical, biological and imaging
125 evaluation of the response to chemotherapy were performed. In case of poor response or bad
126 performance status, three additional cycles of chemotherapy were administered before the
127 surgery. Adjuvant chemotherapy was administered, when feasible, within 2 months after the
128 surgery with carboplatin and paclitaxel until completing a total of six cycles. In case of poor
129 response with important residual disease, two to three cycles of chemotherapy or
130 antiangiogenic maintenance treatment with bevacizumab were added after discussion at the
131 tumor board. To evaluate the accuracy of an expert radiologist for the detection of CLN
132 involvement, all the preoperative CTs had a double lecture by an experienced radiologist of our
133 center (G.B.).

134

135 *2.3. Study data*

136 Medical records were carefully examined, and patient demographic data with particular
137 emphasis on operative records to detail the extent and distribution of the disease spread,
138 surgical procedures, histologic data, and follow-up data were included.

139

140 *2.4. Statistical analysis*

141 Data were summarized by frequency and percentage for categorical variables and by median
142 and range for continuous variables. Comparisons between groups were performed using the
143 Chi-squared or Fisher's exact test for categorical variables and the Mann-Whitney test for
144 continuous variables. Disease-free survival (DFS) was defined as the time from the date of
145 diagnosis until relapse or death, patients alive and disease-free were censored at last follow-up
146 news. Overall survival (OS) was defined as the time from the date of diagnosis until death,
147 patients alive were censored at last follow-up news. Survival data were summarized using the
148 Kaplan-Meier method with their 95% confidence intervals. Univariable analysis was

149 performed using the log-rank test for categorical variable and the Cox model for continuous
150 variable. Multivariable analysis was performed using the Cox model and hazard ratios were
151 estimated with their 95% confidence intervals (CI). Sensitivity and specificity were estimated
152 with their 95% CI (Binomial exact). All reported *p* values were 2-sided. For all the statistical
153 tests, differences were considered significant at 5% level. Statistical analyses were conducted
154 using STATA 13 (StataCorp, Texas, USA) software.

155

156 **3. RESULTS**

157

158 During the study period, 150 patients underwent a complete CRS for frontline treatment of
159 advanced epithelial OC. Of them, 43 (28.7%) underwent CLN resection and 22/43 (51.2%)
160 also received PH disease resection. Metastatic involvement was identified in 17/43 (39.5%)
161 patients. There were not significant differences in baseline characteristics between patients
162 with positive and negative CLN, view Table 1.

163 Table 1. Baseline characteristics of patients with CLN resection.

164 All patients underwent a pelvic peritonectomy, total hysterectomy, bilateral adnexectomy,
165 total infragastric omentectomy and pelvic and paraaortic lymphadenectomy by laparotomy. A
166 complete cytoreduction was achieved in all of them [7]. Patients with positive CLN had a
167 significantly higher PCI and number of affected anatomic regions. CLN involvement was also
168 significantly associated with high scores of Surgical Complexity Score (SCS) of Aletti, large
169 bowel resection and left diaphragm stripping.

170 When analyzing the different regions of PCI, even if not significant, we observed a trend
171 toward more extensive disease in the group of patients with positive CLN, with a higher score
172 of upper abdomen PCI and of small bowel PCI, view Table 2.

173 Table 2. Surgical data of patients with CLN resection.

174 Positive CLN were significantly associated with PH disease and paraaortic lymph node
175 (PALN) involvement. In the same line, the number of PALN affected was higher in patients
176 with CLN involvement, view Table 3.

177 Table 3. Anatomopathological findings of patients with CLN resection.

178 A significantly higher fluid loss (blood plus ascites) during surgery was observed in the
179 patients with CLN involvement with a median (range) of 2300 (332-6860) ml vs. 1257.5
180 (300-3800) ml in patients with negative CLN, $p=0.028$. We did not find significant differences
181 in operative time between the patients with positive and negative CLN with a median (range)
182 of 264 (119-522) minutes and 242 (124-432) minutes, respectively; $p=0.502$. In the same line,
183 there were no differences in the length of hospitalization stay in the two groups with a median
184 (range) of 22 (11-43) days in CLN positive patients vs. 18 (8-93) days in CLN negative
185 patients; $p=0.183$). There were no differences in major surgical complications (grade 3-5)
186 between the two groups of patients (7/17 (41.2%) in CLN positive vs. 6/26 (23.1%) in CLN
187 negative; $p=0.206$).

188 The median overall follow-up was 61.7 months (95% CI = [44.0 – 81.4]). During the study
189 period, 33 (76.7%) out of the 43 patients relapsed, 17/26 (65.4%) in the group with negative
190 CLN and 16/17 (94.1%) in the group of positive CLN. Out of the 9 patients with metastatic
191 lung progression, 7 had positive CLN at diagnosis, just as 4 of the 5 patients with metastatic
192 hepatic relapse. Also, CLN were found to be involved in 5 of the 7 women who had
193 mediastinal lymph node progression. Relapse within the 6 months after the end of the
194 chemotherapy was significantly associated with CLN involvement, 2/26 (7.7%) in the group
195 with negative CLN vs. 8/17 (47.1%) in the group with positive CLN ($p=0.007$).

196 The median DFS for all patients was 19.4 months (95% CI = [13.3 – 25.8]). The median DFS
197 in the group of patients with positive and negative CLN were 11.3 months (95% CI = [8.1 –
198 19.4]) and 25.8 months (95% CI = [18.5 – not reached]), respectively; $p<0.001$. Figure 1

199 displays the DFS curves according to the CLN status.
200 The median OS for all patients was 73.1 months (95% CI = [37.2 – not reached]). The median
201 OS in the group of patients with positive CLN was 31.6 months (95% CI = [16.6 – 80.7]) and
202 in the group with negative CLN it was not reached (95% CI = [48.0 – not reached]); $p=0.007$.
203 Figure 1 shows the OS curves according to the CLN status.

204 Figure 1. Disease-free and overall survivals according to CLN status.

205 In univariable analysis, we found that age, FIGO stage, neoadjuvant chemotherapy, histologic
206 grade, presence of ascites and small bowel PCI were not associated neither with DFS nor with
207 OS; whereas CLN involvement (HR: 3.79, $p<0.001$ and 3.13, $p=0.007$), PCI (HR: 1.12,
208 $p<0.001$ and 1.11, $p=0.002$), upper abdomen PCI (HR: 1.34, $p<0.001$ and 1.35, $p=0.007$) and
209 SCS of Aletti (HR: 1.14, $p=0.027$ and 1.25, $p=0.005$) were significantly associated with DFS
210 and OS, respectively. Confirmed disease at the PH and number of positive PALN were
211 significantly associated with OS and DFS, respectively (Table 4).

212 Table 4. Univariable disease-free and overall survival analysis

213 In multivariable analysis, we included clinically relevant variables. Both CLN involvement
214 (HR: 2.66, 95% CI = [1.14 – 6.21], $p=0.024$) and high PCI (HR:1.11, 95% CI = [1.03 – 1.20],
215 $p=0.008$) were independently associated with decreased DFS, whereas number of positive
216 PALN was not (HR: 0.97, 95% CI = [0.91 – 1.04], $p=0.407$).

217 The sensitivity and the specificity of the re-reading of the CT by an expert radiologist in
218 identifying positive CLN were 76.5% (95% CI = [50.1 – 93.2]) and 52.0% (95% CI = [31.3 –
219 72.2]), respectively. In contrast, the sensitivity and the specificity of the non-expert radiologist
220 were 20.0% (95% CI = [4.3 – 48.1]) and 95.7% (95% CI = [78.1 – 99.9]), respectively.

221 Table 5 summarizes the available studies evaluating the role of CLN resection.

222 Table 5. Available studies assessing the role of CLN resection in patients with advanced
223 epithelial ovarian cancer.

224

225 **4. DISCUSSION**

226

227 Residual tumor after CRS is one of the most important prognostic factors of survival of
228 patients with advanced OC[10–12]. Size of residual tumor has been significantly associated
229 with decreased survival[13]. In the upper abdomen, there are some specific disease sites such
230 as the PH, which can preclude a complete cytoreduction[13–18]. In the last decades, the use
231 of extensive UAP in the surgical approach of OC has significantly increased the rate of
232 optimal primary cytoreduction[2,3]. Our team, as well as other workgroups, demonstrated that
233 resection of enlarged CLN and metastatic disease of the PH was both feasible and with an
234 acceptable morbidity[4,19–22]. However, gynecologic surgeons are often not familiar with
235 this kind of surgical procedure as they are uncommonly required in CRS for OC. Moreover,
236 surgery at the PH requires high level surgical skills as it contains important anatomical
237 structures such as the hepatic artery, the portal vein and the common bile duct. It is possible in
238 these cases to work with an interdisciplinary team in order to achieve complete
239 cytoreduction[20].

240

241 *Incidence of CLN involvement*

242 The real incidence of CLN involvement in patients with advanced epithelial OC is unclear
243 and probably underestimated, as systematic hepato-celiac lymphadenectomy is not performed.
244 In fact, CLN resection is only performed in case of suspicious bulky lymph nodes[22]. In our
245 series, CLN resection was performed when intraoperative suspicious CLN were found. The
246 procedure was done in 28.7% of patients with a complete CRS. Among the patients with CLN
247 resection, 39.5% had CLN involvement. Hence, our estimated incidence of CLN involvement
248 is 11.3% (17/150).

249

250 *Risk factors of CLN involvement*

251 In a retrospective study, Rodriguez et al found that patients requiring UAP due to disease
252 spread at this location had higher preoperative disease overall volume when compared to
253 patients that did not require this kind of procedure[23]. We found similar results in our series,
254 as disease extension measured by the PCI and the number of affected regions was
255 significantly associated with CLN involvement. Disease spread to the upper abdomen was
256 also more frequent in the patients with positive CLN, and left diaphragm stripping was
257 performed more frequently. CLN involvement was also associated with confirmed anatomo-
258 pathological disease in the PH.

259 CLN involvement was significantly associated with large bowel resection and disease spread
260 to small bowel mesentery. In a series of patients undergoing rectosigmoid resection during
261 primary or interval debulking surgery for advanced OC, Gallotta et al. found mesenteric
262 lymph node involvement in 47% of patients. Mesenteric lymph node involvement was
263 associated with depth of bowel infiltration and with isolated celiac trunk or aortic lymph node
264 recurrences[24]. Salani et al. studied the same kind of patients and found that mesenteric
265 involvement was correlated with bowel wall involvement and tumor spread to pelvic and
266 PALN[25]. In the same line, another workgroup found invasion of the muscularis propria and
267 retroperitoneal lymph node metastasis significantly correlated with mesenteric lymph node
268 involvement[26]. Even if we did not evaluate mesenteric lymph node involvement, our results
269 also suggest an increased risk of CLN involvement when disease spreads to the bowel or the
270 mesentery. In fact, a longitudinal pattern of ovarian tumor spread from bowel wall lymphatics
271 through mesenteric lymph nodes and, subsequently, to the upper lymph node stations has
272 already been described[27]. Due to the proximity of the nodes at the base of the mesentery
273 and the retroperitoneum, mesenteric lymph nodes metastasis could spread into the

274 retroperitoneum and ascend along the paraaortic or aortocaval group[28].
275 On the other hand, CLN involvement was associated with PALN involvement. In fact, in our
276 study, all the patients with positive CLN had PALN involvement. Among the patients with
277 CLN involvement, the 71% (12/17) had more than four positive PALN. Our results are
278 biologically plausible as drainage from paraaortic nodes immediately below the left renal vein
279 to the CLN has been demonstrated[29]. Lymphadenectomy in ovarian neoplasm (LION)
280 randomized trial (NCT00712218) aimed to evaluate the impact on overall survival of
281 systematic lymphadenectomy in patients with OC stage IIB-IV undergoing complete PDS
282 with pre and intraoperatively clinical negative lymph nodes. Results presented at the last
283 ASCO meeting showed that microscopic metastases were present in 56% of the patients in
284 LNE arm. Despite this finding, there were not significant differences in OS between the two
285 arms[30]. Our results suggest presence of occult lymph node involvement upper to the renal
286 vein and could explain the absence of benefit of systematic lymphadenectomy in these
287 patients.

288

289 *Prognostic impact of CLN involvement*

290 In our study, CLN involvement was associated with short-term recurrence and resistance to
291 platin-based chemotherapy. We found a gain of DFS and OS in patients with negative CLN.
292 These results are concordant with our previous study, in which disease in the CLN was
293 associated to decreased survival and resistance to chemotherapy in patients with primary and
294 recurrent OC[5]. Furthermore, CLN involvement was found to be a high-risk marker for
295 metastatic and mediastinal lymph node progression. More than 80% of patients with hepatic
296 or lung metastasis at recurrent disease had positive CLN.
297 In multivariable analysis, high PCI and CLN involvement were both independently associated
298 with decreased DFS. Even if residual tumor has a more important prognostic impact than

299 initial extent of tumor burden[1], our series showed that in patients with complete
300 cytoreduction, PCI remained an independent risk factor of decreased DFS. These findings are
301 similar to other studies. The survival benefit obtained by an optimal cytoreduction seemed to
302 decrease with increasing initial tumor volume[31]. In a previous study, our workgroup found
303 that complex surgical procedures involving two or more visceral resections, tumor volume an
304 d extension of the disease before surgery decreased survival rates[32].

305 Patients with different degree of disease extension to the upper abdomen and patients with
306 positive CLN are both included in stage IIIC of FIGO classification. Other authors have
307 suggested to modify current FIGO staging system[33]. We believe that FIGO stage IIIC
308 should be subdivided depending on criteria like PCI score or CLN status in order to define a
309 subgroup with a poorer prognosis. Due to their poor prognosis, another option would be to
310 consider patients with CLN involvement as a FIGO stage IVB, analogously to patients with
311 cardiophrenic lymphatic involvement, which are currently included in this subgroup
312 stage[34].

313 Benefit of extensive CRS procedures in CLN positive patients remains unclear. In our study,
314 patients with CLN involvement underwent more complex procedures with higher median
315 Aletti SCS when compared to patients with negative CLN. There were no differences in
316 surgical postoperative complications depending on CLN status, but the overall rate of
317 postoperative major complications was high (13/43 – 30.2%). Extensive procedures have a
318 non-negligible morbidity and can decrease patient's quality of life[2,35–38].

319 Patients with CLN involvement have poor prognosis even after complete CRS. Medical
320 personalized strategies with new target therapies may be a way to improve their outcome. It
321 would be interesting to identify these patients preoperatively to tailor the optimal surgical
322 timing and to intensify treatment modalities. We found a good sensitivity (77%) for the
323 detection of CLN involvement by the double lecture of the CT performed by an expert

324 radiologist, while the sensitivity of a non-expert radiologist was poor (20%). The low
325 specificity of the expert radiologist could be explained by the enlargement of the reactive
326 CLN, probably due to tumoral burden.

327 The main limitations of our study are its unicentric retrospective design and the small sample
328 size. However, even if CLN resection is an uncommon procedure in surgical approach of
329 advanced OC, the population of our study is homogeneous as all patients were primary
330 diagnosed of advanced epithelial OC and underwent a complete cytoreduction, which can
331 allow to better assess survival of these patients. Another important strength of this study is the
332 long follow-up of our patients.

333

334 **5. CONCLUSION**

335

336 CLN involvement and high PCI score are independently associated with a decreased DFS
337 after complete CRS for OC. CLN involvement is a marker of diffuse disease and an
338 independent risk factor for early recurrent disease. Medical personalized strategies with new
339 target therapies may be the best option to improve survival in these patients. These findings
340 should be confirmed in further prospective and multicentric studies.

341 **REFERENCES**

342

343 [1] Eisenkop SM, Spirtos NM, Friedman RL, Lin WCM, Pisani AL, Peticucci S. Relative
344 influences of tumor volume before surgery and the cytoreductive outcome on survival
345 for patients with advanced ovarian cancer: A prospective study. *Gynecol Oncol*
346 2003;90:390–6. doi:10.1016/S0090-8258(03)00278-6.

347 [2] Chi DS, Franklin CC, Levine DA, Akselrod F, Sabbatini P, Jarnagin WR, et al.
348 Improved optimal cytoreduction rates for stages IIIC and IV epithelial ovarian,
349 fallopian tube, and primary peritoneal cancer: A change in surgical approach. *Gynecol*
350 *Oncol* 2004;94:650–4. doi:10.1016/j.ygyno.2004.01.029.

351 [3] Chi DS, Eisenhauer EL, Zivanovic O, Sonoda Y, Abu-Rustum NR, Levine DA, et al.
352 Improved progression-free and overall survival in advanced ovarian cancer as a result
353 of a change in surgical paradigm. *Gynecol Oncol* 2009;114:26–31.
354 doi:10.1016/j.ygyno.2009.03.018.

355 [4] Martinez A, Pomel C, Mery E, Querleu D, Gladieff L, Ferron G. Celiac lymph node
356 resection and porta hepatis disease resection in advanced or recurrent epithelial
357 ovarian, fallopian tube, and primary peritoneal cancer. *Gynecol Oncol* 2011;121:258–
358 63. doi:10.1016/j.ygyno.2010.12.328.

359 [5] Martínez A, Pomel C, Filleron T, De Cuypere M, Mery E, Querleu D, et al. Prognostic
360 relevance of celiac lymph node involvement in ovarian cancer. *Int J Gynecol Cancer*
361 2014;24:48–53. doi:10.1097/IGC.0000000000000041.

362 [6] Sugarbaker PH. Peritonectomy procedures. *Ann Surg* 1995;221:29–42.

363 [7] Gilly FN, Cotte E, Brigand C, Monneuse O, Beaujard AC, Freyer G, et al. Quantitative
364 prognostic indices in peritoneal carcinomatosis. *Eur J Surg Oncol* 2006;32:597–601.
365 doi:10.1016/j.ejso.2006.03.002.

- 366 [8] Aletti GD, Santillan A, Eisenhauer EL, Hu J, Aletti G, Podratz KC, et al. A new frontier
367 for quality of care in gynecologic oncology surgery: Multi-institutional assessment of
368 short-term outcomes for ovarian cancer using a risk-adjusted model. *Gynecol Oncol*
369 2007;107:99–106. doi:10.1016/j.ygyno.2007.05.032.
- 370 [9] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new
371 proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*
372 2004;240:205–13. doi:10.1097/01.sla.0000133083.54934.ae.
- 373 [10] Bristow BRE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Maximal
374 Cytoreductive Surgery for Advanced Ovarian Carcinoma During the Platinum Era :
375 2002;20:1248–59. doi:10.1200/JCO.2002.20.5.1248.
- 376 [11] Bois A Du, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of
377 surgical outcome as prognostic factor in advanced epithelial ovarian cancer: A
378 combined exploratory analysis of 3 prospectively randomized phase 3 multicenter
379 trials: by the arbeitsgemeinschaft gynaekologische onkologie studien-gruppe
380 ovarialkarzin. *Cancer* 2009;115:1234–44. doi:10.1002/cncr.24149.
- 381 [12] Winter WE, Maxwell GL, Tian C, Carlson JW, Ozols RF, Rose PG, et al. Prognostic
382 factors for stage III epithelial ovarian cancer: A Gynecologic Oncology Group study. *J*
383 *Clin Oncol* 2007;25:3621–7. doi:10.1200/JCO.2006.10.2517.
- 384 [13] Heitz F, Harter P, Alesina PF, Walz MK, Lorenz D, Groeben H, et al. Pattern of and
385 reason for postoperative residual disease in patients with advanced ovarian cancer
386 following upfront radical debulking surgery. *Gynecol Oncol* 2016;141:264–70.
387 doi:10.1016/j.ygyno.2016.03.015.
- 388 [14] Eisenkop SM, Spirtos NM. What are the current surgical objectives, strategies, and
389 technical capabilities of gynecologic oncologists treating advanced epithelial ovarian
390 cancer? *Gynecol Oncol* 2001;82:489–97. doi:10.1006/gyno.2001.6312.

- 391 [15] Salani R, Axtell A, Gerardi M, Holschneider C, Bristow RE. Limited utility of
392 conventional criteria for predicting unresectable disease in patients with advanced stage
393 epithelial ovarian cancer. *Gynecol Oncol* 2008;108:271–5.
394 doi:10.1016/j.ygyno.2007.11.004.
- 395 [16] Bristow RE, Duska LR, Lambrou NC, Fishman EK, O’Neill MJ, Trimble EL, et al. A
396 model for predicting surgical outcome in patients with advanced ovarian carcinoma
397 using computed tomography. *Cancer* 2000;89:1532–40.
- 398 [17] Axtell AE, Lee MH, Bristow RE, Dowdy SC, Cliby WA, Raman S, et al. Multi-
399 institutional reciprocal validation study of computed tomography predictors of
400 suboptimal primary cytoreduction in patients with advanced ovarian cancer. *J Clin*
401 *Oncol* 2007;25:384–9. doi:10.1200/JCO.2006.07.7800.
- 402 [18] Nougaret S, Addley HC, Colombo PE, Fujii S, Al Sharif SS, Tirumani SH, et al.
403 Ovarian Carcinomatosis: How the Radiologist Can Help Plan the Surgical Approach.
404 *RadioGraphics* 2012;32:1775–800. doi:10.1148/rg.326125511.
- 405 [19] Raspagliesi F, Ditto A, Martinelli F, Haeusler E, Lorusso D. Advanced ovarian cancer:
406 Omental bursa, lesser omentum, celiac, portal and triad nodes spread as cause of
407 inaccurate evaluation of residual tumor. *Gynecol Oncol* 2013;129:92–6.
408 doi:10.1016/j.ygyno.2013.01.024.
- 409 [20] Song YJ, Lim MC, Kang S, Seo SS, Kim SH, Han SS, et al. Extended cytoreduction of
410 tumor at the porta hepatis by an interdisciplinary team approach in patients with
411 epithelial ovarian cancer. *Gynecol Oncol* 2011;121:253–7.
412 doi:10.1016/j.ygyno.2010.12.350.
- 413 [21] Tozzi R, Traill Z, Garruto Campanile R, Ferrari F, Soleymani Majd H, Nieuwstad J, et
414 al. Porta hepatis peritonectomy and hepato–celiac lymphadenectomy in patients with
415 stage IIIC–IV ovarian cancer: Diagnostic pathway, surgical technique and outcomes.

- 416 Gynecol Oncol 2016;143:35–9. doi:10.1016/j.ygyno.2016.08.232.
- 417 [22] Gallotta V, Ferrandina G, Vizzielli G, Conte C, Lucidi A, Costantini B, et al.
418 Hepatoceliac Lymph Node Involvement in Advanced Ovarian Cancer Patients :
419 Prognostic Role and Clinical Considerations. Ann Surg Oncol 2017.
420 doi:10.1245/s10434-017-6005-1.
- 421 [23] Rodriguez N, Miller A, Richard SD, Rungruang B, Hamilton CA, Bookman MA, et al.
422 Upper abdominal procedures in advanced stage ovarian or primary peritoneal
423 carcinoma patients with minimal or no gross residual disease: An analysis of
424 Gynecologic Oncology Group (GOG) 182. Gynecol Oncol 2013;130:487–92.
425 doi:10.1016/j.ygyno.2013.06.017.
- 426 [24] Gallotta V, Fanfani F, Fagotti A, Chiantera V, Legge F, Alletti SG, et al. Mesenteric
427 lymph node involvement in advanced ovarian cancer patients undergoing rectosigmoid
428 resection: Prognostic role and clinical considerations. Ann Surg Oncol 2014;21:2369–
429 75. doi:10.1245/s10434-014-3558-0.
- 430 [25] Salani R, Diaz-Montes T, Giuntoli RL, Bristow RE. Surgical management of
431 mesenteric lymph node metastasis in patients undergoing rectosigmoid colectomy for
432 locally advanced ovarian carcinoma. Ann Surg Oncol 2007;14:3552–7.
433 doi:10.1245/s10434-007-9565-7.
- 434 [26] Baiocchi G, Cestari LA, MacEdo MP, Oliveira RAR, Fukazawa EM, Faloppa CC, et al.
435 Surgical implications of mesenteric lymph node metastasis from advanced ovarian
436 cancer after bowel resection. J Surg Oncol 2011;104:250–4. doi:10.1002/jso.21940.
- 437 [27] O’Hanlan KA, Kargas S, Schreiber M, Burrs D, Mallipeddi P, Longacre T, et al.
438 Ovarian carcinoma metastases to gastrointestinal tract appear to spread like colon
439 carcinoma: Implications for surgical resection. Gynecol Oncol 1995;59:200–6.
440 doi:10.1006/gyno.1995.0008.

- 441 [28] Mcdaniel P, Varma GK, Granfield J. Pictorial Essay Pathways of Nodal Cecum ,
442 Ascending CT Demonstration Metastasis in Carcinomas of the Colon , and Transverse
443 Colon : 1993.
- 444 [29] Hirai I, Murakami G, Kimura W, Nara T, Dodo Y. Long descending lymphatic pathway
445 from the pancreaticoduodenal region to the para-aortic nodes: its laterality and
446 topographical relationship with the celiac plexus. *Okajimas Folia Anat Jpn*
447 2001;77:189–99.
- 448 [30] Harter P, Sehouli J, Lorusso D, Reuss A, Vergote I, Marth C. LION: Lymphadenectomy
449 in ovarian neoplasms—A prospective randomized AGO study group led gynecologic
450 cancer intergroup trial. *J Clin Oncol* [Internet] 2017;35:5500. Available from:
451 <http://ascopubs.org/doi/abs/>.
- 452 [31] Zivanovic O, Sima CS, Iasonos A, Hoskins WJ, Pingle PR, Leitao MMM, et al. The
453 effect of primary cytoreduction on outcomes of patients with FIGO stage IIIC ovarian
454 cancer stratified by the initial tumor burden in the upper abdomen cephalad to the
455 greater omentum. *Gynecol Oncol* 2010;116:351–7. doi:10.1016/j.ygyno.2009.11.022.
- 456 [32] Martinez A, Ngo C, Leblanc E, Gouy S, Luyckx M, Darai E, et al. Surgical Complexity
457 Impact on Survival After Complete Cytoreductive Surgery for Advanced Ovarian
458 Cancer. *Ann Surg Oncol* 2016;23:2515–21. doi:10.1245/s10434-015-5069-z.
- 459 [33] Menczer J. Is there a revision needed of the current FIGO staging system? *Acta Obstet*
460 *Gynecol Scand* 2017;96:1159–61. doi:10.1111/aogs.13193.
- 461 [34] Prader S, Harter P, Grimm C, Traut A, Waltering KU, Alesina PF, et al. Surgical
462 management of cardiophrenic lymph nodes in patients with advanced ovarian cancer.
463 *Gynecol Oncol* 2016;141:271–5. doi:10.1016/j.ygyno.2016.03.012.
- 464 [35] Rafii A, Stoeckle E, Jean-Laurent M, Ferron G, Morice P, Houvenaeghel G, et al.
465 Multi-center evaluation of post-operative morbidity and mortality after optimal

466 cytoreductive surgery for advanced ovarian cancer. *PLoS One* 2012;7:e39415.
467 doi:10.1371/journal.pone.0039415.

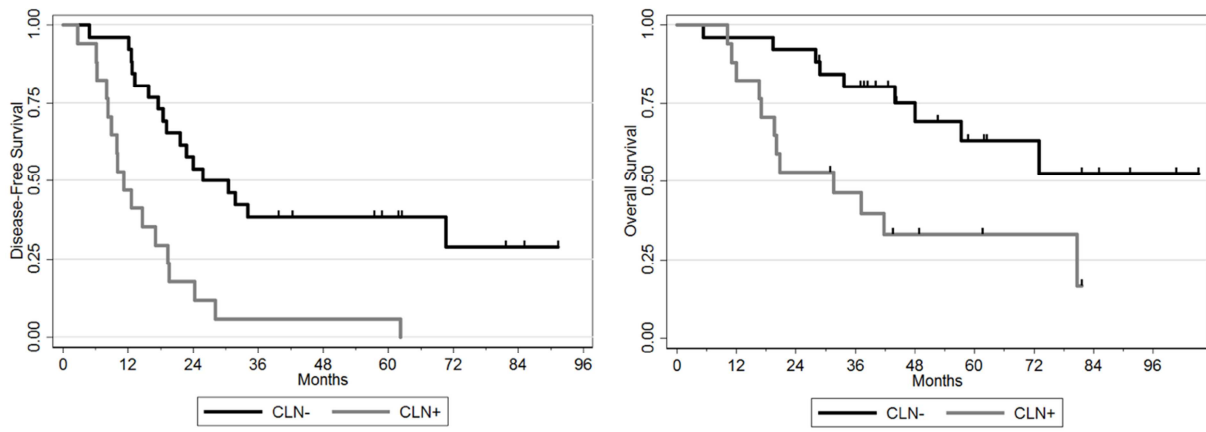
468 [36] Nieuwenhuyzen-de Boer GM, Gerestein CG, Eijkemans MJC, Burger CW, Kooi GS.
469 Nomogram for 30-day morbidity after primary cytoreductive surgery for advanced
470 stage ovarian cancer. *Eur J Gynaecol Oncol* 2016;37:63–8.

471 [37] Chi DS, Zivanovic O, Levinson KL, Kolev V, Huh J, Dottino J, et al. The incidence of
472 major complications after the performance of extensive upper abdominal surgical
473 procedures during primary cytoreduction of advanced ovarian, tubal, and peritoneal
474 carcinomas. *Gynecol Oncol* 2010;119:38–42. doi:10.1016/j.ygyno.2010.05.031.

475 [38] Schulman-Green D, Ercolano E, Dowd M, Schwartz P, Mccorkle R. Quality of life
476 among women after surgery for ovarian cancer. *Palliat Support Care* 2008;6:239–47.
477 doi:10.1017/S1478951508000497.

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1 Figure 1. Disease-free and overall survivals according to celiac lymph node status.



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1 **Table 1. Baseline characteristics of patients with celiac lymph node resection.**

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	Overall n=43	Negative CLN n=26	Positive CLN n=17	<i>p</i> - value
Age (years) median (range)	61 (22-75)	60 (22-74)	65 (48-75)	0.115
BMI (kg/m²) median (range)	23 (16.6- 37.1)	22.9 (16.6- 33.8)	24 (18.8- 37.1)	0.345
WHO performance status classification n (%)				
0	23 (53.5)	15 (57.7)	8 (47.1)	0.494
≥1	20 (46.5)	11 (42.3)	9 (52.9)	
Preoperative CA-125 (UI/ml) median (range) <i>Missing</i>	857 (13- 15000) 7	722.5 (13- 15000) 4	1365 (47- 3000) 3	0.846
FIGO stage n (%)				
IIIc	36 (83.7)	23 (88.5)	13 (76.5)	0.407
IV	7 (16.3)	3 (11.5)	4 (23.5)	

3

4 CLN: celiac lymph nodes

5 BMI: body mass index

6 WHO: World Health Organization

7 CA-125: cancer antigen 125

8 FIGO: International Federation of Gynecology and Obstetrics

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Table 2. Surgical data of patients with celiac lymph node resection.

	Overall n=43	Negative CLN n=26	Positive CLN n=17	<i>p</i> - value
Type of surgery n (%)				
Upfront	18 (41.9)	10 (38.5)	8 (47.1)	0.576
Interval	25 (58.1)	16 (61.5)	9 (52.9)	
Intraoperative findings				
PCI median (range) <i>Missing</i>	22 (5-33) 2	17 (5-28) 1	25.5 (10-33) 1	0.011
Upper abdomen PCI median (range) <i>Missing</i>	7 (0-9) 2	6 (0-9) 1	8 (2-9) 1	0.157
Small bowel PCI median (range) <i>Missing</i>	2 (0-8) 2	2 (0-7) 1	3 (0-8) 1	0.098
No. affected anatomic regions median (range) <i>Missing</i>	11 (3-13) 2	10 (3-13) 1	11 (7-13) 1	0.040
Ascites (ml) median (range)	200 (0-5000)	150 (0-4500)	1000 (0-5000)	0.087
Surgical procedures n (%)				
Small bowel resection	4 (9.3)	2 (7.7)	2 (11.8)	1.000
Large bowel resection	22 (51.2)	9 (34.6)	13 (76.5)	0.007
If large bowel resection, rectosigmoid resection [n=22]	18 (81.8)	6 (66.7)	12 (92.3)	0.264
Multiple bowel resection	6 (14)	3 (11.5)	3 (17.6)	0.666
Right diaphragm stripping	40 (93)	23 (88.5)	17 (100)	0.266
Left diaphragm stripping	23 (53.5)	10 (38.5)	13 (76.5)	0.015
If diaphragm stripping, diaphragm resection [n= 40]	11 (27.5)	7 (30.4)	4 (23.5)	0.730
Liver resection	2 (4.7)	2 (7.7)	0	0.510
Cholecystectomy	17 (39.5)	10 (38.5)	7 (41.2)	0.859
Lesser omentum resection	33 (76.7)	18 (69.2)	15 (88.2)	0.269
PH resection	22 (51.2)	11 (42.3)	11 (64.7)	0.151
Splenectomy	27 (62.8)	14 (53.8)	13 (76.5)	0.133
Distal pancreatectomy	8 (18.6)	5 (19.2)	3 (17.6)	1.000
Partial gastrectomy	3 (7)	2 (7.7)	1 (5.9)	1.000
Extended peritonectomy	37 (86)	20 (76.9)	17 (100)	0.066
Glissonectomy	6 (14)	4 (15.4)	2 (11.8)	1.000
Mesentery or bowel vaporization	13 (30.2)	8 (30.8)	5 (29.4)	0.925
Partial abdominal wall resection	7 (16.3)	3 (11.5)	4 (23.5)	0.407
Aletti Score median (range)	10 (4-16)	9 (4-14)	12 (7-16)	0.011

11

- 12 CLN: celiac lymph nodes
- 13 PCI: peritoneal cancer index
- 14 Upper abdomen PCI: sum of 1 (right upper), 2 (epigastrium) and 3 (left upper) regions score
- 15 Small bowel PCI: sum of 9 (upper jejunum), 10 (lower jejunum), 11 (upper ileum) and 12 (lower
- 16 ileum) regions score
- 17 PH: porta hepatis
- 18 Extended peritonectomy: peritonectomy of more than three abdominal regions

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Table 3. Anatomopathological findings of patients with celiac lymph node resection.

	Overall n=43	Negative CLN n=26	Positive CLN n=17	<i>p</i> - value
Anatomopathological findings				
Histologic subtype n (%)				
Serous high grade	33 (76.7)	19 (73.1)	14 (82.4)	1.000
Serous low grade	7 (16.3)	4 (15.4)	3 (17.6)	
Endometrioid	1 (2.3)	1 (3.8)	0	
Mixed	1 (2.3)	1 (3.8)	0	
Carcinosarcoma	1 (2.3)	1 (3.8)	0	
Chemotherapy Response Score [n=25] n (%)				
Type 1: no or minimal tumor response	10 (40%)	4 (25%)	6 (66.7%)	0.238
Type 2: partial tumor response	10 (40%)	8 (50%)	2 (22.2%)	
Type 3: near-complete tumor response	4 (16%)	3 (18.8%)	1 (11.1%)	
Type 3': complete tumor response	1 (4%)	1 (6.3%)	0	
No. CLN removed median (range)	2 (1-6)	2.5 (1-6)	2 (1-6)	0.872
No. positive CLN median (range)	0 (0-5)	0 (0-0)	1 (1-5)	
PH confirmed disease n (%)	17 (39.5)	7 (26.9)	10 (58.8)	0.037
PALN involvement n (%)	31 (72.1)	14 (53.8)	17 (100)	0.002
No. positive PALN median (range)	3 (0-24)	1.5 (0-13)	5 (1-24)	0.001
> 4 positive PALN n (%)	19 (44.2)	7 (26.9)	12 (70.6)	0.009

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CLN: celiac lymph nodes
Chemotherapy Response Score developed by Böhm et al.
PH: porta hepatis
PALN: paraaortic lymph nodes

26 **Table 4. Univariable disease-free and overall survival analysis**
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	Disease-free survival			Overall survival		
	HR	95% CI	<i>p</i> -value	HR	95% CI	<i>p</i> -value
Age (years)	1.02	[0.98-1.05]	0.330	1.03	[0.98-1.08]	0.200
FIGO stage IV	0.63	[0.24-1.64]	0.342	0.39	[0.09-1.68]	0.189
Neoadjuvant CT	1.15	[0.58-2.30]	0.687	0.98	[0.41-2.36]	0.967
PCI	1.12	[1.05-1.19]	<0.001	1.11	[1.04-1.18]	0.002
Upper abdomen PCI	1.34	[1.13-1.58]	<0.001	1.35	[1.09-1.68]	0.007
Small bowel PCI	1.05	[0.91-1.21]	0.508	1.05	[0.89-1.24]	0.564
Ascites (dl)	1.02	[0.99-1.04]	0.171	1.00	[0.97-1.04]	0.930
Aletti Score	1.14	[1.02-1.29]	0.027	1.25	[1.07-1.47]	0.005
High histologic grade	0.73	[0.29-1.83]	0.507	1.07	[0.29-3.96]	0.919
Positive CLN	3.79	[1.87-7.69]	<0.001	3.13	[1.31-7.49]	0.007
No. positive PALN	1.06	[1.01-1.11]	0.027	1.04	[0.97-1.11]	0.242
PH confirmed disease	1.93	[0.97-3.83]	0.057	2.36	[0.99-5.64]	0.047

28
 29 HR: hazard ratio
 30 FIGO: International Federation of Gynecology and Obstetrics
 31 CT: chemotherapy
 32 PCI: peritoneal cancer index
 33 Upper abdomen PCI: sum of 1 (right upper), 2 (epigastrium) and 3 (left upper) regions score
 34 Small bowel PCI: sum of 9 (upper jejunum), 10 (lower jejunum), 11 (upper ileum) and 12 (lower
 35 ileum) regions score
 36 CLN: celiac lymph nodes
 37 PALN: paraaortic lymph nodes
 38 PH: porta hepatis
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40 Table 5. Available studies assessing the role of CLN resection in patients with advanced epithelial
 41 ovarian cancer.
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Author and year	Disease of included patients	Number of patients included in the study n	Number of patients with CLN or PH disease resection n	Number of patients with reported histopathological disease in CLN or PH n (%)	Morbidity related to CLN or PH disease resection n (%)	Prognostic outcome of patients with disease in CLN or PH
Song et al. 2011	Primary and recurrent epithelial ovarian cancer	155	11 (PH disease resection)	11 (100) with PH disease	0 (0)	median PFS 8 months (range 1-13)
Martinez et al. 2011	Primary and recurrent epithelial ovarian cancer	28	28 (CLN and/or PH disease resection)	15/26 (57.7) with CLN involvement 19/28 (67.9) with PH disease	1 (3.6)	-
Raspagliesi et al. 2013	FIGO stage IIIC-IV epithelial ovarian cancer	37	5 (CLN resection) 4 (PH disease resection)	5 (100) with CLN involvement 4 (100) with PH disease	2 (5.4)	-
Martinez et al. 2014	Primary and recurrent epithelial ovarian cancer	41	41 (CLN and/or PH disease resection)	23 (56.1) with CLN involvement	-	median PFS 9 months (95% CI [5-16]) median OS 27 months (95% CI [9-40])
Tozzi et al. 2016	FIGO stage IIIC-IV epithelial ovarian cancer	216	31 (CLN and/or PH disease resection)	31 (100) with PH disease and/or CLN involvement	0 (0)	-
Gallotta et al. 2017	FIGO stage IIIC-IV epithelial ovarian cancer	85	85 (CLN resection)	45 (52.9%) with CLN involvement	0 (0)	median PFS 16 months (95% CI [12-19]) median OS 43 months (95% CI [32-54])

Angeles et al. 2019	FIGO stage III-IV epithelial ovarian cancer	43	43 (CLN resection)	17 (39.5)	0 (0)	median DFS 11 months (95% CI [8-19]) median OS 32 months (95% CI [17-81])
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- 44 CLN: celiac lymph node involvement
- 45 PH: porta hepatis
- 46 PFS: progression-free survival
- 47 CI: confidence interval
- 48 OS: overall survival
- 49 DFS: disease-free survival