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ORIGINAL ARTICLE

Standard versus extended lymphadenectomy in radical surgical treatment for pancreatic head carcinoma

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Summary

Purpose: *The primary aim of this study was to evaluate the benefit of extended lymphadenectomy in pancreaticoduodenectomy (PD) and to estimate its impact on long-term survival in patients with pancreatic head carcinoma. Secondary endpoints included perioperative mortality, postoperative morbidity and predictors of survival in patients undergoing standard versus extended lymphadenectomy for pancreatic head carcinoma.*

Methods: *From January 2007 to December 2010, 60 patients with potentially resectable pancreatic head carcinoma were operated using pylorus-preserving pancreatoduodenectomy (PPPD) at the Clinic for Digestive Surgery, Clinical Center of Serbia, Belgrade. Intraoperatively patients were randomly stratified into two groups: the first group (N1=30) underwent PPPD with standard lymphadenectomy whilst the second group (N2=30) was operated with PPPD with extended lymphadenectomy. None of the patients received adjuvant treatments.*

Results: *The number of retrieved lymph nodes, mean operating time and postoperative hospital stay were greater in patients with extended lymphadenectomy . Cox regression analysis showed that stage and lymph node metastasis were independent prognostic factors for survival.*

Conclusion: *Extended lymphadenectomy in PPPD did not improve long-term survival in patients with resectable pancreatic head carcinoma and led to comparable and similar morbidity and mortality rates to those after standard lymphadenectomy.*

Key words: *lymphadenectomy, pancreatic head carcinoma, pancreatoduodenectomy*

Introduction

The idea of extended lymphadenectomy was based on the fact that lymph nodes outside the field of dissection can harbor micrometastases [1]. Fortner's concept of regional pancreatectomy [2] had a major influence on Japanese surgeons which led to a whole new movement and approach in radical cancer treatment in the leading centers in Japan since the 1980s. In the studies of Ishikawa and Manabe, long-term survival was significantly improved in patients who underwent pancreatoduodenectomy (PD) with extended lymphadenectomy comparing to those with standard lymphadenectomy [3,4]. Since then, the benefits of extended lymphadenectomy and extended radical PD have been evaluated in retrospective studies in Japan and also in Western countries. Long-term survival did not differ significantly in patients with extended lymphadenectomy compared to those with standard lymphadenectomy, but some studies showed significantly higher rates of postoperative complications in patients who underwent PD with extended lymphadenectomy [5]. The

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first randomized clinical trial (RCT) to compare the results of standard vs extended lymphadenectomy in PD was reported by Pedrazzoli et al. [6]. In that trial patients who underwent PD with extended lymphadenectomy had a significantly better long-term survival, but this concerned only patients with lymph node metastasis (N1). Three other RCTs failed to repeat Pedrazzoli's results and did not prove benefit in long-term survival in patients with extended lymphadenectomy in PD for patients with pancreatic head carcinoma [7-9]. Other results concerning mortality, morbidity and quality of life were similar between groups or even worse in patients with extended radical PD. Standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma was finally defined in a consensus statement by the International Study group on pancreatic surgery (ISGPS) in 2014 [10].

The primary endpoint of this study was to evaluate the benefit of extended lymphadenectomy in PD and to estimate its impact on long-term survival in patients with pancreatic head carcinoma. Secondary endpoints included mortality and morbidity in patients undergoing standard vs extended lymphadenectomy in PD for pancreatic head carcinoma.

Methods

In this study we enrolled patients younger than 80 years of age with potentially resectable adenocarcinoma of the pancreatic head, excluding mucinous cystadenocarcinoma and intraductal papillary mucinous carcinoma. Other exclusion criteria included distant visceral metastases, tumor involvement of the major blood vessels and surrounding organs, ASA (American Society of Anesthesiologists) score higher than 3 and any adjuvant therapy previously received. This study was approved by institutional ethical review board and all patients gave written informed consent before they were enrolled in the study.

From January 2007 to December 2010, 60 patients with potentially resectable pancreatic head carcinoma were enrolled and resected using PPPD at the Clinic for Digestive Surgery, Clinical Center of Serbia, Belgrade. Patients were intraoperatively randomly stratified in two groups: in the first group (N1=30) patients underwent PPPD with standard lymphadenectomy and in the second group (N2=30) they were subjected to PPPD with extended lymphadenectomy. No patient had received preoperatively biliary drainage and also no patient had received neoadjuvant therapy.

Surgery

PPPD was used as a standard surgical procedure in all patients. Resection margins of the pancreatic body and the bile duct had to be confirmed as tumor-free by frozen section to complete R0 resection. Combined resections of major blood vessels and surrounding organs were not performed in any patient.

Standard lymphadenectomy included removal of the anterior and posterior pancreatoduodenal lymph nodes (13a, 13b, 17a, 17b), lymph nodes of the right side of the hepatoduodenal ligament (12b1, 12b2, 12c), lymph nodes to the right side of the superior mesenteric artery from its origin to the inferior pancreaticoduodenal artery (14a,14b) and lymph nodes of the anterior-superior region of the common hepatic artery (8a).

Extended lymphadenectomy included removal of all lymph nodes along the common and proper hepatic artery (8a,8p), lymph nodes around the celiac trunk (9), all lymph nodes of the left and right side of the hepatoduodenal ligament (12b1, 12b2, 12c+12a1, 12a2, 12p1,12p2), circumferential skeletonisation of the superior mesenteric artery between the aorta and the inferior pancreaticoduodenal artery (14a, 14b+14c, 14d) and lymph nodes of the anterolateral aspect of the aorta and of the inferior vena cava, in continuity with Gerota's fascia, between the celiac axis and the inferior mesenteric artery (Figure 1). The above lymph node station nomenclature was defined according to the General Rules for Surgical and Pathological Studies on Cancer of the Pancreas by the Japan Pancreas Society [11].

Histopathology

Histopathological examination of the resected specimens was performed at the Department of Pathology, Clinic for Digestive Surgery. The stage of disease of the resected patients was classified according to the UICC-TNM Classification (6th Edn).

Staging

Ultrasonography (US) and multiple detector com-

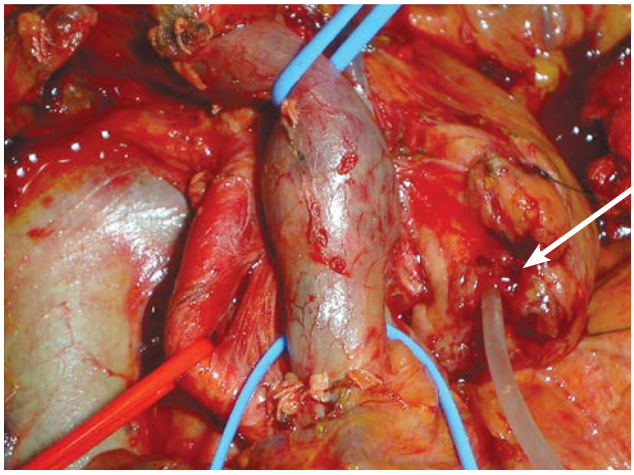

Figure 1. Extended lymph node dissection - circumferential skeletonisation of the superior mesenteric artery (SMA) (left); portal vein pulled to the right (middle); transected pancreas with catheter placed in the pancreatic duct (right) (arrow).

Figure 2. CT-scan showing tumor mass in the head of the pancreas (arrow).

puted tomography (MDCT) (Figure 2) were performed prior to surgery in order to preoperatively determine the stage of disease, thus giving help to identify potentially resectable patients.

Biochemical investigations

Serum bilirubin and other biochemical parameters were measured using a classical biochemistry analyzer, Olympus AU400 (CLIAwaived.com) San Diego, USA, while serum level of CA 19-9 was measured by two-step commercial immune assay for clinical practice (ARCHITECT) (Abbott Laboratories Abbott Park, IL, USA).

Patient survival

Mortality was defined as any death related to surgery that occurred within 30 days from surgery. The patients were followed monthly during first 6 months, every 3 months until one year from surgery and every 6 months thereafter.

Table 1. Patient age in the two groups

Lymphadenectomy	*Years*
Extended	59.70
Median	59.50
SD	6.979
Minimum	39
Maximum	74
IQR	9
Standard	64.47
Median	65.00
SD	4.925
Minimum	48
Maximum	73
IQR	7

Statistics

In order to observe all the clinical and laboratory features in the studied population, we used the following methods of descriptive statistics: a) measures of central tendency; the arithmetic mean (X) and the median (MED); b) measures of variability; the variation interval (max-min), standard deviation (SD) and the interquartile range (IQR); and c) relative numbers. To determine the statistical significance of the differences, averages or median of the clinical and laboratory findings in patients who underwent standard or radical lymphadenectomy, we used Student's t-test for unbounded samples or Mann-Whitney U test, depending on the normality of the distribution of tested features. Chi square test was used to analyze the statistical significance of differences in representation of the category features of the patients who underwent standard or radical lymphadenectomy. Analysis of the patient survival of was conducted using the Kaplan-Meier's analysis, with log rank test for comparison of survival of the patients who underwent standard or radical lymphadenectomy. For analysis of predictors of mortality, Cox's regression hazard model was used.

Results

The demographic characteristics between the two groups were well balanced. The mean patient age (59.7±9.3 vs 64.5±6.1 years) and gender distribution (male/female 16/14 vs 18/12, x^2=1.071; p>0.05) were similar (Tables 1 and 2).

Comorbidity rates (23.6 vs 30%) were not significantly different between the two groups. Preoperative serum bilirubin level (329.6 vs 354.6 nmol/L; t=1.081; p>0.05) and CA 19-9 level (407.2 vs 395.5 kU/L; t=0.380; p>0.05) were also similar between groups. The mean operative time (305±58.3 vs 446±135.2 min, t=13.463; p<0.01) was significantly longer in the extended operation group (Figure 3).

The mean number of retrieved lymph nodes in the standard and extended group were 18.5±5 vs 24.1±6.5, t=7.110; p<0.01 (Figure 4) which was statistically highly significant.

Table 2. Gender distribution in the two groups

Gender	*Extended N (%)*	*Standard N (%)*	*Total N (%)*
Male	14 (46.7)	18 (60.0)	32 (53.3)
Female	16 (53.3)	12 (40.0)	28 (46.7)
Total	30 (100.0)	30 (100.0)	60 (100.0)

x^2=1.071, p>0.05

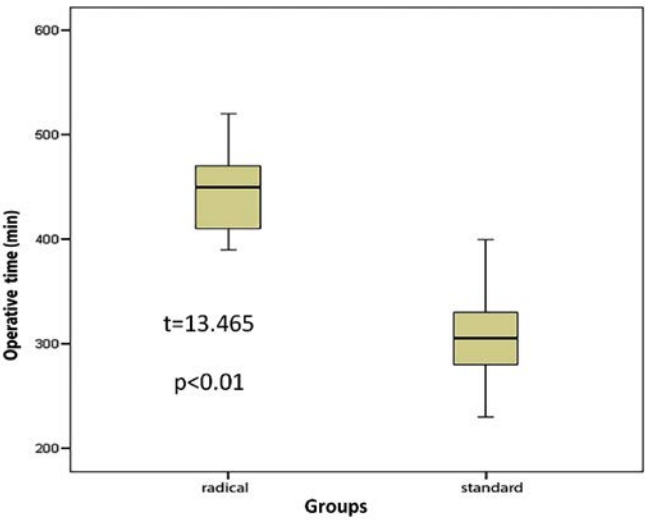

Figure 3. Mean operative time in the two groups.

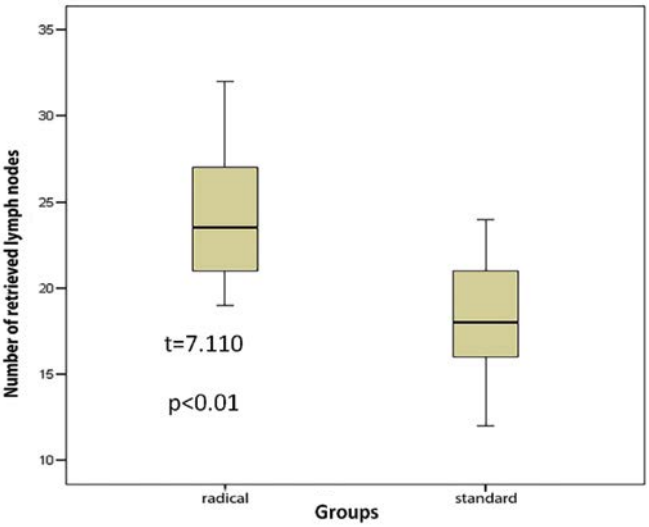

Figure 4. Mean number of retrieved lymph nodes between the two groups.

Table 3. Distribution of lymph node metastasis in the two groups

Lymph node group	*Prevalence of metastasis – Standard* %	*Prevalence of metastasis – Extended* %
13-posterior pancreatoduodenal	43.3	36.7
17-anterior pancreatoduodenal	30.0	33.3
8-hepatic artery	20.0	16.7
12-hepatoduodenal ligament	10.0	16.7
14-superior mesenteric artery	16.7	13.3
16-para-aortic	0	16.7

x^2=0.278, p>0.05

The duration of postoperative gastric suction (7.5 vs 8 days) was comparable in the two groups. The incidence of early postoperative bleeding (0 vs 3.3%, x^2=1.017; p>0.05), relaparotomy (3.3 vs 6.7%, x^2=0.351; p>0.05) and mortality rate (3.3 vs 6.7%, x^2=0.351, p>0.05) were similar between the two groups. One patient in the extended lymphadenectomy group had an early postoperative bleeding from the gastroduodenal artery and was reoperated the same day. He died on the first postoperative day from complications of massive myocardial infarction. Another patient from the extended group was reoperated on the 12th postoperative day due to complicated pancreatic fistula and total pancreatectomy was performed. He died from septic complications 9 days later. One patient from the standard group was reoperated on the 16th postoperative day due to pancreatic fistula and near-total pancreatectomy was performed. Six days later the patient died from septic complications as a result of gram-negative bacterial sepsis. Postoperative hospital stay (17.9 vs 21.7 days, t=2.480; p<0.05) was significantly longer in the extended operation group.

Pancreatic fistula rates (13.3 vs 23.3%, x^2=1.002, p>0.05) were similar between groups as expected since we used standard "duct-to-mucosa" technique in the creation of pancreatico-jejunostomy in all patients. Delayed gastric emptying (DGE) was registered in 2 patients (6.7%) in standard and in 6 patients (20%) in extended operation group (x^2=2.308, p>0.05). Higher incidence of DGE in the extended group was probably due to more extensive peripancreatic nerve tissue clearance.

The majority of patients in both groups had T3 tumors (53.3 vs 56.7%). T-status distribution was similar between the 2 groups (x^2=2.422, p>0.05). Median survival in T1-T2 patients was 29.8 months and 24.3 months in patients with T3-T4 tumor. There were no 5-year survivors in the T3-T4 group.

Lymph node metastasis was present in 17 patients (56.7%) in each group. Details of nodal status in all 60 patients are shown in Table 3.

The highest prevalence of lymph node metastasis was found at the anterior and posterior pancreatoduodenal nodes (13 and 17) which were removed by both standard and extended lymphadenectomy. The next higher prevalence of metastasis was found in lymph nodes along the

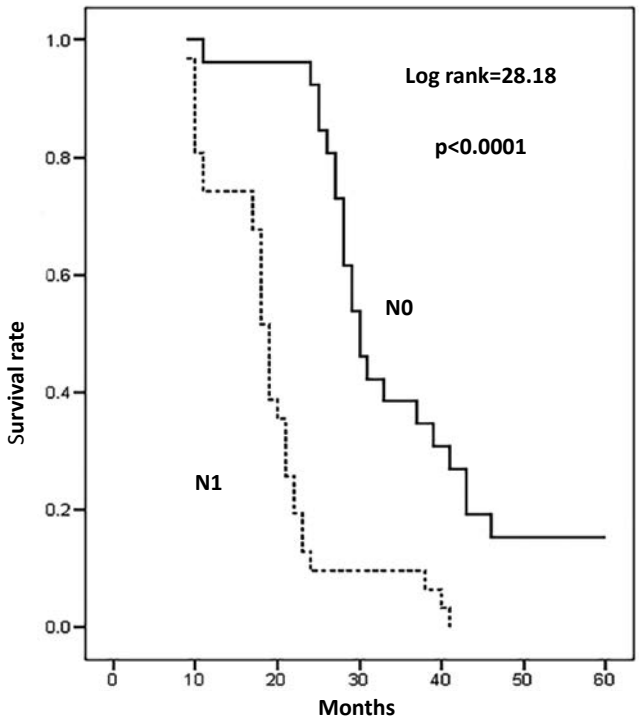

Figure 5. 5-year survival curves in N0/N1 patients.

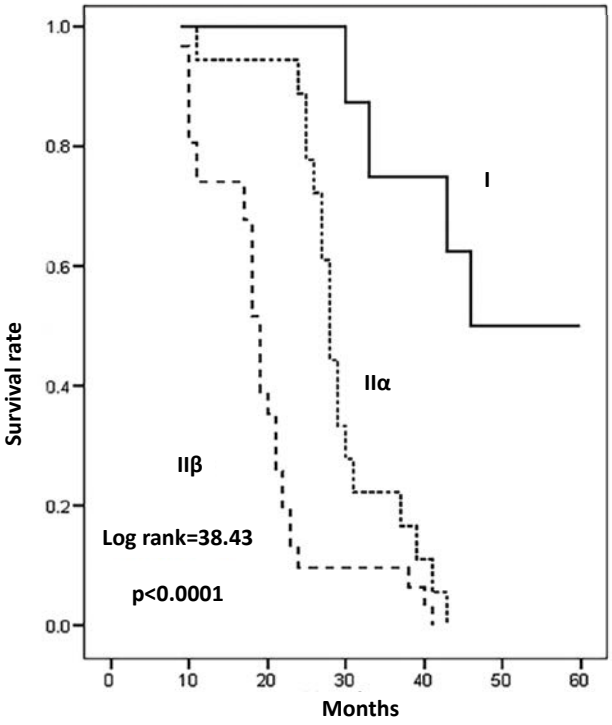

Figure 6. 5-year survival between the two groups.

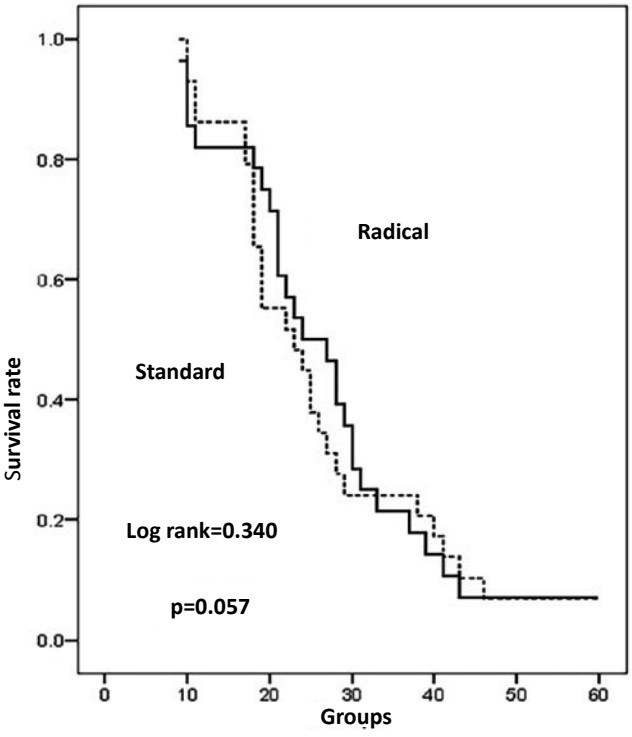

Figure 7. 5-year survival according to disease stage.

hepatic artery (8) and those in the hepatoduodenal ligament (12) and those around the superior mesenteric artery (SMA) (14). The 5-year survival for negative-node patients was 15.4% (4 patients) while none of the patients with lymph node metastasis survived 5 years (0%) (x^2=28.7; p<0.01) (Figure 5). Median survival time for the negative-node patients was 35.4 months and 18.3 months (log rank=28.18, p<0.0001) in patients with lymph node metastasis.

No difference was found between the 2 groups in stage (I/IIa/IIb/III/IV: 3/10/17/0/0 vs 5/9/14/2/0, x^2=0.583, p>0.05). The 5-year survival rate for stage I, IIa and IIb/III patients was 50, 0 and 0% respectively (x^2=35.5, p<0.01) (Figure 4). The median survival for stage I, IIa and IIb/III patients was 49, 29.3 and 19.3 months, respectively. The incidence of lymphatic, venous and neural invasion was similar between groups (80, 70 and 50% vs 90, 66.7 and 60%).

The 5-year OS for all patients was 7.0%. Median OS for all patients was 26.6 months. More than 80% of the patients died within 2 years after surgery. There were 4 patients surviving for 5 years, 2 in each group. All of these 4 patients had stage I disease. The overall 5-year survival rate for the standard lymphadenectomy group was 6.9% and 7.1% for the extended lymphadenectomy group (x^2=0.086,p>0.05). Median overall survival in the standard group was 26.3 months comparing to 27 months in the extended operation group (p>0.05; Figure 5).

Uni- and multivariate Cox regression analysis was performed to identify the predictors of survival. In univariate analysis lymphatic invasion, venous invasion, lymph node metastasis, stage and resection margin were identified as prognos-

tic factors. In multivariate Cox regression analysis stage and lymph node metastasis were shown to be independent prognostic factors.

Discussion

Pancreatic carcinoma remains a rapidly progressive and fatal disease with high case-fatality ratio. Potentially curative resection can be done in 10-20% of patients of which the majority will develop disease recurrence within a year after surgery. Median survival time after surgery is 14.3 months [12]. The 5-year survival is 14-20% in high-volume centers and 30% for lesions less than 3cm. More than 50% of all investigated patients had T3 tumors at the time of diagnosis. Lymph node metastases are present in 60-90% of the patients [13,14] and metastases in para-aortic lymph nodes in 16-26% [15]. The 1-, 2- and 3-year survival in patients with positive para-aortic lymph nodes are 30, 7 and 3% respectively [15]. High incidence of lymph node metastasis confirmed as microscopically positive retroperitoneal margin (R1) is the main reason for early recurrence of the disease and its poor prognosis. This could support the hypothesis that more aggressive surgical approaches including extended lymphadenectomy, resections of adjacent involved surrounding organs and vascular resection could improve long-term survival in patients resected for pancreatic head carcinoma. Multivisceral resections and vein resections (portal vein-inferior mesenteric vein) are justified if it means obtaining tumor-free resection margins.

The question of extensiveness of lymphadenectomy is quite complex and has remained a subject of controversies among surgeons for more than three decades. The value of extended lymphadenectomy in PD for pancreatic head carcinoma has been evaluated by many retrospective studies and 4 RCT. The study of Pedrazzoli et al. showed improved survival for patients undergoing extended lymphadenectomy in the subset of patients with positive lymph node metastasis. Other 3 RCTs did not demonstrate any survival benefit for positive-node patients undergoing extended lymphadenectomy. In our study we also concluded that extended lymphadenectomy in radical PD for pancreatic head carcinoma could not improve the long-term survival of the resected patients (6.9 vs 7.1%). All types of postoperative complications between the two groups were similar. The mean operative time (305 vs 446 min, $p<0.01$) was significantly longer in the extended operation group in this study. Postoperative hospital stay (17.9 vs 21.7 days, $p<0.05$) was also significantly longer in the extended operation group. The 5-year OS for all patients was 7%. Four patients survived for 5 years and all of them had stage I disease. Median OS in the standard operation group was 26.3 months comparing to 27 months in the extended operation group. Median OS was 26.6 months in all patients. The 5-year survival rate in node-negative patients was 15.4% and 0% in node-positive patients. Median survival for node-negative patients was 35.4 months and 19.2 months in node-positive patients. It is clear that lymph node metastasis is an independent prognostic factor. Recently published systematic reviews and meta-analysis including the 3 published RCTs concluded that extended lymphadenectomy does not benefit survival [16,17]. In our study we also came to the conclusion that extended lymphadenectomy does not improve long-term survival of the resected patients. In 2014 the International Study Group on Pancreatic Surgery reached a consensus agreement on the extent of lymphadenectomy which should be done in the surgical treatment of pancreatic head carcinoma [10]. They made a clear definition and consensus on which lymph node groups should be included in the lymphadenectomy for pancreatic cancer. Therefore, lymphadenectomy should include: LN stations 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a right lateral side, 14b right lateral side, 17a and 17b. However, no strong recommendation could be given on resecting LN 8p and 16b routinely.

Although a R0 resection is usually said to be the only chance of long-term survival in these patients, it is now clear that this treatment modality alone is not efficient enough and should be combined with some form of adjuvant chemotherapy with or without radiotherapy.

Conflict of interests

The authors declare no confict of interests.

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