Adjuvant chemotherapy for resected duodenal adenocarcinoma: a case-matched analysis in nation wide cohort

Jacob de Bakker (j.debakker@vumc.nl)
VU medisch centrum https://orcid.org/0000-0002-3017-0882
L.L. Meijer
Amsterdam UMC - Locatie VUMC: Amsterdam UMC Locatie VUmc
B.M. Zonderhuis
Amsterdam UMC VUMC Site: Amsterdam UMC Locatie VUmc
H.J. van der Vliet
Amsterdam UMC VUMC Site: Amsterdam UMC Locatie VUmc
F. Daams
Amsterdam UMC VUMC Site: Amsterdam UMC Locatie VUmc
N.C.T. van Grieken
Amsterdam UMC VUMC Site: Amsterdam UMC Locatie VUmc
B.I. Lissenberg-Witte
Amsterdam UMC VUMC Site: Amsterdam UMC Locatie VUmc
G. Kazemier
Amsterdam UMC VUMC Site: Amsterdam UMC Locatie VUmc

Research Article

Keywords: Duodenal, adenocarcinoma, resected, adjuvant, chemotherapy

Posted Date: March 15th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1437649/v1

Abstract

Background

Duodenal adenocarcinoma (DA) is a rare tumor for which survival data on adjuvant chemotherapy in patients after surgical treatment are unclear. This case-matched study in a nationwide cohort aims to investigate the benefit of adjuvant chemotherapy for patients with resectable DA on overall survival.

Methods

All patients diagnosed with DA and intestinal type periampullary adenocarcinoma (PVA) in the Netherlands between 2000 and 2015 were included (n=1316). Patients with disease stage II and III who underwent resection and adjuvant chemotherapy were matched (1:2), based on identified covariates associated with OS, with patients who underwent surgery alone. Overall survival was compared using Kaplan-Meier estimates.

Results

The median OS was 49.9 months in patients who underwent curative resection (n=649). Univariate and multivariate analysis showed a significant influence of age, lymph node involvement, and T- stage on survival. The group of patients receiving adjuvant treatment consisted of 43 patients and the non-adjuvant group of 83 case matched patients. The median OS of the complete matched cohort (n=126) was 26.9 months. No statistically significant survival benefit was found for the adjuvant group as compared to the group treated with surgery alone (median OS=34.4 months and 23.0 months, *P*=0.20).

Conclusion

This population-based, case-matched analysis demonstrates no statistically significant survival benefit for adjuvant chemotherapy after curative resection in stage II and III patients. Future studies with specified treatment regimens as well as thorough stratification for prognostic factors will be required in order to more definitively determine the role of adjuvant therapy.

1. Introduction

Duodenal adenocarcinoma (DA) is a rare tumor, which constitutes less than 0.5% of all gastrointestinal malignancies[1]. It represents the majority of tumors developing in the small bowel and is therefore often classified as small bowel adenocarcinoma[2]. A previous study showed many similarities in terms of DNA copy number alterations in duodenal carcinoma and colorectal carcinomas[3]. This resemblance could be relevant to optimize clinical decision making and treatment in patients with DA[4, 5]. It was hypothesized that that adjuvant treatment in node positive resectable duodenal adenocarcinoma could be of clinical benefit for patients similar to colorectal cancer (CRC) patients. Since intestinal type periampullary adenocarcinoma (PVA) and DA both display an intestinal histopathological phenotype and reported survival rates appear to be comparable PVA is also included in this study[6]. Currently, the only curative

treatment for DA is resection of the primary tumor[7]. Depending on tumor location, pancreaticoduodenectomy for proximal tumors and segmental resection for distal DA is the first choice of treatment. Both techniques have demonstrated equal outcomes when radical resection is feasible, resulting in a 5-year overall survival (OS) of approximately 50%[8]. One of the prognostic factors that is reported to negatively influence survival after curative resection is lymph node involvement[8–10].

If (neo)adjuvant treatment is used in patients with DA, various therapeutic options are used in current practice, including adjuvant chemotherapy (often fluorouracil-based combined with a platinum analog) [7], radiotherapy [11],or combined chemo- and radiotherapy[12]. Adjuvant therapy after curative resection is common practice for several intestinal tumor types, particularly colon cancer[13–15]. The merits of adjuvant systemic treatment after resection of the primary tumor in patients with DA however have never been studied in a randomized clinical trial. Performing such trials is challenging due to low incidence of DA. Previous non-randomized studies described use of adjuvant therapy in the whole group of patients with small bowel carcinomas, including DA. These studies have shown equivocal outcomes on the additional benefit of adjuvant chemotherapy[16–18]. A recently published meta-analysis of those studies from our group did not reveal a significant benefit for patients treated with adjuvant chemotherapy[8]. This analysis included heterogeneous studies in which adjuvant therapy regimens were not stratified for prognostic factors. It could be argued that, in line with patients suffering from colorectal carcinoma (CRC), adjuvant chemotherapy might only be beneficial to a subgroup of DA patients with poor prognostic factors, such as lymph node involvement[13, 19]. Therefore, despite the increasing use of adjuvant chemotherapy after curative resection of DA, the true benefit of adjuvant therapy on survival remains debatable. In The Netherlands, all newly diagnosed malignancies are registered in a population-based database. In the current study, we aimed to investigate the impact of adjuvant systemic therapy on overall survival (OS) in patients after curative resection of DA and PVA in stage II and III using this nation-wide registry.

2. Methods

2.1

Netherlands with histologically proven DA or PVA who underwent curative resection of the primary tumor between January 2000 and December 2015 were included in this study. Patients with pancreatico-biliary type cancer of the papilla of Vater or metastatic tumors located in the duodenum were excluded. All adenocarcinomas were classified according to the TNM classification, AJCC edition 5–7[20].

Data were retrieved from The Netherlands Cancer Registry (NCR). The NCR is a nationwide registry comprising population-based data on all newly diagnosed patients with malignancies in The Netherlands notified by data from the Dutch nationwide pathological archive (PALGA). These data are included in the NCR as well as data from the National Registry of Hospital Discharge Diagnosis. The NCR is maintained prospectively and all data is stored anonymously. This study was approved by the review board of the NCR.

2.2 Clinical characteristics

Prospective data collection included demographical variables, clinical characteristics, including age, sex, histopathology, primary treatment, including type of surgical resection, tumor stage, adjuvant therapy and palliative treatment. For survival analysis, the dates of last follow-up or death were collected.

The primary outcome was OS. This was calculated from the date of diagnosis to the date of last follow-up or death. Patients who were alive at their last follow-up were censored. No data were available on surgery related deaths. Adjuvant therapy was defined by administration of any type of single-agent or combination of chemotherapy after the primary resection. Missing data were excluded from analysis.

2.3 Statistical analysis

Descriptive statistics were used to describe patient and tumor characteristics for both the unselected cohort, as well as for the case-matched cohort. Descriptive statistics are presented as frequencies for categorical variables and median with range for continuous variables. Clinical characteristics were compared using a Chi-Square test for categorical data and an independent sample t-test for continuous variables, as appropriate. Overall survival was estimated by Kaplan-Meier curves.

Factors possibly associated with survival in all patients who underwent curative resection were identified by univariate and multivariate analysis with Cox regression models. Patients in stage II and III receiving either adjuvant chemotherapy or no adjuvant therapy were matched in a 1:2 ratio by age, sex, involvement of lymph nodes, and type of resection. Matching in a 1:2 ratio was done to increase statistical power. Patients were only included for matching if there was a match according to the above-mentioned factors mentioned. Patients were excluded for the case-matched analysis if any of the matched variables was unavailable. After case matching, OS of patients treated with adjuvant therapy was compared to patients receiving no adjuvant therapy by Kaplan-Meier curves with log-rank test for statistical significance.

All data are expressed as median with range, unless normally distributed, in which case mean +/- standard deviation was reported. Statistical significance was defined as a *P*-value < 0.05. All analyses were performed using the statistical package SPSS 22.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1 Patient demographics of the unmatched cohort

Between 2000 and 2015, a total of 1316 patients were treated for DA or PVA in The Netherlands, of whom 649 patients (49%) underwent curative resection. The patient's characteristics of all resected patients are summarized in Table 1. The median age of all patients was 66 years (range: 27–93 years) and 53.2% was male. Type of resection of the primary tumor was divided into four groups: pylorus preserving pancreaticoduodenectomy (PPPD), non-pylorus preserving pancreaticoduodenectomy (NPPPD),

segmental resection and other type of resection, such as endoscopic removal. Of these 649 patients, 99 patients underwent PPPD, 318 NPPPD, 93 segmental resection and 139 another type of surgery. Five patients underwent curative resection of the primary tumor combined with resection of synchronous liver metastases, one concurrent with resection of peritoneal metastasis and one with resection of pelvic lymph nodes. These seven patients were not included in the analysis. Of all patients undergoing curative resection (n = 649), 43 (6.7%) patients received adjuvant chemotherapy in stage II and III, 3 (0.5%) patients received neo-adjuvant chemo(radio)therapy, 4 (0.6%) patients received adjuvant chemo-radiotherapy. No patients received only radiotherapy.

Table 1

Demographic characteristics of all the patients included in the curative cohort.

		n = 649
Age	Years, median (range)	66 (27–93)
Sex (%)	Male	345 (53)
Type of surgery (%)	PPPD	318 (49)
	Non PPPD	99 (15)
	Segmental resection	93 (14)
	Other	139 (22)
T-stage (%)	1	99 (15)
	2	119 (18)
	3	230 (36)
	4	189 (29)
	Unknown	12 (2)
Lymph node involvement (%)	No	288 (44)
	Yes	304 (47)
	Unknown	57 (9)
Stage (%)*	I	154 (24)
	II	235 (36)
	III	222 (34)
	IV	33 (5)
	Unknown	5 (1)
Chemotherapy (%)	Neoadjuvant	6 (1)
	Adjuvant	51 (8)
	None	592 (91)
Tumor Differentiation (%)	Good	42 (6)
	Medium	320 (49)
	Poor	169 (26)

PPPD: pylorus preserving pancreaticoduodenectomy, *Non PPPD* : non-pylorus preserving pancreaticoduodenectomy, *Other*: other type of resection, * AJCC 7th edition

		n = 649
	Unknown	118 (19)

PPPD: pylorus preserving pancreaticoduodenectomy, *Non PPPD* : non-pylorus preserving pancreaticoduodenectomy, *Other*: other type of resection, * AJCC 7th edition

3.2 Adjuvant therapy in the unmatched cohort

The median OS of all patients after curative resection was 49.9 months. Univariate and multivariate analysis showed a significant influence of age, lymph node involvement and T- stage on survival (**Table 2**). Of the 43 patients treated with adjuvant chemotherapy in stage II and III, 37 patients (86.0%) had positive lymph nodes, compared to 257 (43.9%) of the patients undergoing resection without adjuvant therapy. Of the 43 patients treated with adjuvant chemotherapy, 35 patients (81.3%) had T3-4 stage, compared to 371 (63.3%) of the patients who underwent resection without adjuvant therapy. No data were available on type, combination and timing of adjuvant therapy.

Table 2. Univariate analysis in curative cohort

		Number	HR	95% CI	*P*
Age	Year +1		1.030	1.020-1.040	< 0.001*
Sex	Male	345	0.856	0.695-1.054	0.143
Type of surgery	Other type	318	referent		
	PPPD	99	0.844	0.601-1.184	0.326
	Non PPPD	93	0.950	0.702-1.285	0.738
	Segmental resection	139	0.799	0.533-1.197	0.277
Lymph node involvement	No	288	referent		
	Yes	304	2.652	2.103-3.344	< 0.001*
T-Stage	1	78	referent		
	2	109	0.952	0.625-1.450	0.082
	3	220	1.571	1.113-2.216	0.010*
	4	181	2.319	1.641-3,277	< 0.001*
Tumor Differentiation	Good	42	referent		
	Medium	320	0.988	0.621-1.571	0.959
	Poor	169	1.360	0.845-2.191	0.206

Multivariate analysis in curative cohort

		Number	HR	95% CI	*P*
Age	Year +1		1.032	1.021-1.042	< 0.001*
Lymph node involvement	No	288	referent		
	Yes	304	2.287	1.785-2.929	< 0.001*
T-Stage	1	78	referent		
	2	109	0.748	0.471-1.189	0.220
	3	220	1.079	0.734-1.587	0.699
	4	181	1.624	1.088-2.424	0.018*

PPPD: pylorus preserving pancreaticoduodenectomy, *Non PPPD* : non-pylorus preserving pancreaticoduodenectomy, *Other*: other type of resection, *HR*: Hazard Ratio, *95% CI* : 95% Confidence Interval, *P*: P value

3.3 Effect of adjuvant therapy in the case-matched cohort

To correct for possible clinical factors associated with administration of adjuvant therapy, patients receiving adjuvant chemotherapy in stage II and III (the adjuvant group, n = 43) were matched 1:2 with patients receiving surgery without adjuvant chemotherapy (the non-adjuvant group, n = 83). The clinico-pathological characteristics of the patients are shown in Table 3. As a consequence of the matching, no difference in age, sex, type of surgery, tumor stage, and the presence of lymph node involvement were found between these two groups.

Table 3
Demographic characteristics of the matched cohort

		Adjuvant	Non Adjuvant
		n = 43	**n = 83**
Age	Years,median(range)	61 (40–79)	62 (38–83)
Sex (%)	Male	20 (46)	38 (46)
Type of surgery (%)	PPPD	5 (12)	13 (15)
	Non PPPD	31 (72)	57 (70)
	Segmental resection	3 (7)	6 (7)
	Other type	4 (9)	7 (8)
Lymph node involvement (%)	No	5 (12)	10 (12)
	N1	31 (72)	57 (68)
	N2	7 (16)	16 (20)
Stage (%)	I	none	none
	II	5 (12)	10 (12)
	III	38 (88)	73 (88)
	IV	none	none
Tumor Differentiation (%)	Well	1 (2)	5 (6)
	Moderatly	20 (46)	44 (53)
	Poorly	14 (33)	29 (35)
	Unknown	8 (19)	5 (6)

PPPD: pylorus preserving pancreaticoduodenectomy, *Non PPPD* : non-pylorus preserving pancreaticoduodenectomy, *Other*: other type of resection,

The median OS of the complete matched cohort (i.e. $n = 126$) was 26.9 months. No statistically significant survival benefit was found for the adjuvant group as compared to surgery alone (median OS = 34.4 months and 23.0 months, $P = 0.20$, Fig. 1). In the adjuvant group 1-, 3-, and 5-year OS rates were 93.0%, 453.4.2%, and 37.2% respectively. In the non-adjuvant group, 1-, 3-, and 5-year OS rates were 69.1%, 42.1%, and 34.99% respectively.

Over the past 15 years, an increase in administration of adjuvant chemotherapy was observed. Between 2000–2005, four patients were treated with adjuvant chemotherapy, compared to 14 patients between

2006–2010 and 25 patients between 2011–2015. However, an increased incidence of DA and PVA was also found during these years of 154, 178, and 317 patients, respectively.

4. Discussion

This population-based, case-matched analysis demonstrates no significant survival benefit for adjuvant chemotherapy after curative resection of DA and PVA. Although patients treated with adjuvant therapy more often demonstrated poor prognostic factors such as lymph node involvement, no benefit for adjuvant therapy was found after case-matching. The OS did not differ significantly between patients receiving adjuvant chemotherapy and patients not receiving adjuvant chemotherapy.

This is the first study to explore the role of adjuvant chemotherapy in a nation-wide analysis of all patients with only DA and PVA presenting over a period of 15 years. PVA was included due to its resemblance with DA on its intestinal histopathological phenotype and reported survival rates[6]. Our study focusses only on DA and PVA and excluded patients with pancreaticobiliary type papilla of Vater carcinoma since OS is more favorable in patients with intestinal type tumors compared to pancreaticobiliary type tumors[6, 21]. This is reflected in a median survival of 60 months vs 17 months respectively (P = 0.002)[6]. DA and PVA are presumed to be comparable to small bowel adenocarcinomas (SBAs) and CRC by many authors[2, 17]. In patients suffering from CRC, administration of adjuvant therapy is mostly based on disease stage and poor prognostic factors. In patients with CRC administration of adjuvant chemotherapy is standard of care in case of positive lymph nodes after resection of the primary tumor (i.e. stage III disease) or high risk stage II disease[19].

The putative benefit of adjuvant therapy after curative resection has been a topic for debate in DA. In line with the current results, another population-based retrospective analysis found no benefit for the use of adjuvant chemotherapy[22]. Adjuvant chemotherapy after curative resection also demonstrated no survival benefit in patients with SBA, including DA. However, combining all patients with SBA together and heterogeneity of the reported adjuvant treatment regimens could bias these results[17, 23]. In contrast, there are also studies that show a possible benefit of adjuvant therapy in patients with SBA. Ecker et al. found a significant survival benefit in patients who received adjuvant chemotherapy in SBA (HR 1.36 CI 1.24–1.50, P < 0.001) and also a significant difference in OS in stage III duodenal adenocarcinoma (median OS 34.1 vs 24.3 months, P = 0.002)[16]. Legué et al. showed a significant survival benefit in patients who received adjuvant chemotherapy in SBA with a median survival of 66 months compared to 48 months (P = 0.034). No subgroup analysis for patients with DA was performed and information on the chemotherapy treatment schedules that were used lacked in both studies[2, 16]. Thus, adjuvant therapy for DA remains at least doubtful.

The open label BALLAD trial (NCT02502370) is currently open for patient accrual [24] and aims to determine the potential benefit of two different adjuvant chemotherapy schedules in patients with resected SBA (including DA) stage I, II and III. In the future, the results of this trial could potentially aid to also determine the benefit of adjuvant therapy for patients with DA if a subgroup analysis for patients

with DA will be performed. This is relevant as a worse 5-year survival was reported in DA compared to adenocarcinomas located in jejunum or ileum (28.1%, 50.9% and 42.8% respectively)[2].

Legué et al. reported different 5-year crude survival rates for patients with tumors on different locations of the primary tumor in the small bowel for duodenum, jejunum and ileum[2].

Besides adjuvant chemotherapy, the combination of chemotherapy and radiotherapy was not found to improve survival in the analysis performed by Ecker et al. However, the addition of radiotherapy was often based on poor prognostic factors compromising interpretation[12, 25].

Multiple chemotherapeutic regimens are currently in use for (metastatic) SBA. Mostly, fluorouracil-based regimens are used, either alone or combined with a platinum analog. A significant survival benefit was reported for fluorouracil-based regimens combined with a platinum analog compared to other types of chemotherapy[26]. And in addition, the combination of capecitabine and oxaliplatin (CAPOX) improved response rates and overall survival in SBA and advanced and metastatic ampullary adenocarcinoma[27].

Several limitations of this study warrant emphasis, especially regarding the retrospective study design of this nation-wide registration. The data collection could be influenced by data omission and miscoding during the data collection process. Case matching was performed to ensure equal groups for survival analysis, but this case matching could not control for variables which are not registered in the NCR. In our registry, several important prognostic factors were not reported, including resection margins, tumor perforation, performance status, surgical complications, the specific type of chemotherapy used and data on disease free survival. Positive margins have been associated with poorer survival outcomes and could e.g. have affected the use of adjuvant chemotherapy but also the lack of information on the other parameters may have resulted in bias because of unbalanced matching

In conclusion, this case–matched cohort study demonstrated no statistically significant survival benefit for the use of adjuvant chemotherapy in patients with DA and PVA after curative-intent surgical resection of the primary tumor. The lack of specified treatment regimens withholds a final conclusion on the potential benefit specified per treatment regimen. Differences in the 1-, and 3 year OS rates were notable and in favor of the use of adjuvant chemotherapy, but did not reach statistical significance.

Future studies with specified treatment regimens as well as thorough stratification for prognostic factors could help to unravel the true role of adjuvant therapy in patients with DA and PVA.

Declarations

i. Funding (information that explains whether and by whom the research was supported)

Not applicable

ii. Conflicts of interest/Competing interests (include appropriate disclosures)

Not applicable'

iii. Ethics approval (include appropriate approvals or waivers)

This retrospective study was granted by de Ethic approval board

iv. Consent to participate (include appropriate statements)

Not applicable

v. Consent for publication (include appropriate statements)

Not applicable'

vi. Availability of data and material (data transparency)

All data is available upon request

vii. Code availability (software application or custom code)

Not applicable'

viii. Authors' contributions

JK de Bakker and L Meijer were responsible for data collection. All authors contributed equally to this

manuscript for analysis of data and writing the manuscript

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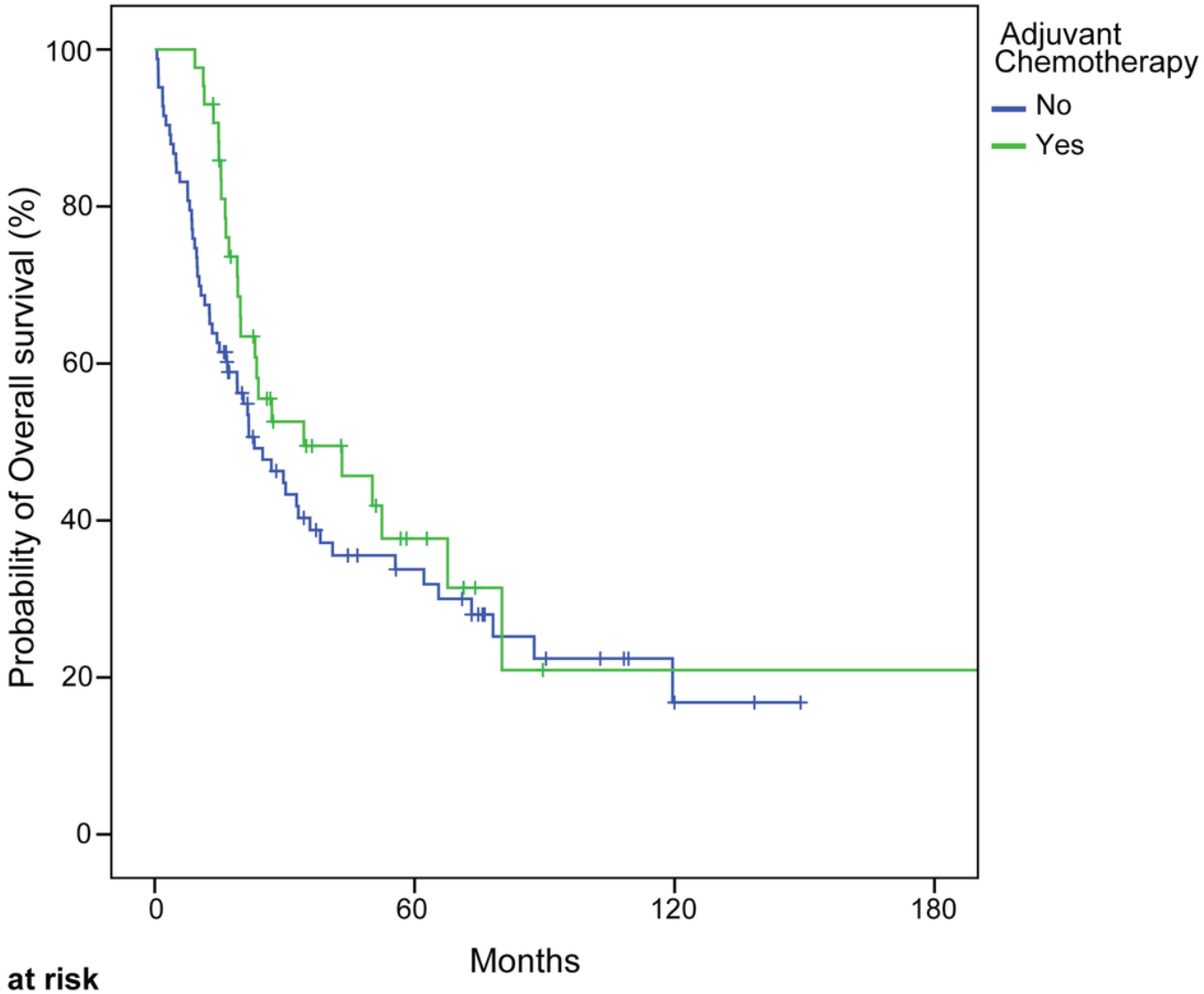
Figures



Number at risk

Adjuvant	43	7	2	0
Non-adjuvant	83	18	2	0

Figure 1

Impact of adjuvant therapy compared to resection alone on overall survival in the case-matched cohort with resected DA and PVA. There was no significant difference in OS between both groups (P=0.20). Kaplan-Meier curves are shown.