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Research Article

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Surgical Therapy of Ductal Adenocarcinoma of the Pancreas Head: Real World Data from an Excellence Center

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Abstract

Introduction: The 5-year survival rates of surgical therapy in adenocarcinoma of the pancreas (PHAC) head varies widely, in the last years many studies showed partial astounding improvement in survival by more radical and/or concomittant systemic therapies. 167 patients with PHAC with and without systemic treatment were operated by Whipple- or pylorus - preserving procedures in our Center of Excellence. These "Real- World-Data" may help to identfy the significance of surgical therapy within present pancreas carcinoma therapy options.

Methods and results: 167 patients with PHAC underwent surgery in Munich at Clinic and Polyclinic of Surgery of the Technical University, Clinical Center "Rechts der Isar" from August 2014 to June 2023. These prolective collected data were retrospectively evaluated by a multivariate analysis. The different parameters were independently associated with overall survival. Median age at surgery was 70 years and 53.9% were male and 46.1% were female. Systemic therapy was additionally performed in 71.3% of all patients. The median overall survival (OS) of the entire population was 19.4 months. For patients who received systemic therapy the median OS was 23 months. Significant predictors of survival were the resection status (R0/R1), lymphe node involvement (N0/ypN0/N1/ypN1/pN2/ypN2), distant metastasis (M0/M1), CRM-status (CRM-/CRM+), tumor stage (IA/IV), lymphnode invasion, vascular infiltration (venous/arterial) and resection of the V. mesenterica. Tumor progress or relapse were found in most cases locally (66.9%) and/or in the liver (40%). The median time to tumor progression was 6.4 months and was diagnosed in 43% at 12 months and in 74% at 24 months. The 5-year OS was 10.1% and the 1-year survival was 67.4% for all patients with surgical resection, respectively 6.7% and 72.5% for patients with systemic therapy and resection.

Conclusion: Despite varoius systemic therapies and more locally radical operation procedures the value of surgical therapy could improve the prognosis only in few patients for a limitited period. Even more radical surgical therapy was not able to decrease effectively significant risk factors for local recurrence like CRM-involvement, R-status or lymphnode involvement. Most of the patients developed local recurrence after a short postoperative time interval. In our study systemic therapy and resection had an short-time effect for survival, after 2 years there was no difference between resected and resected and systemic treated patients. The question if radical surgery may improve the patients prognosis stays at least open, local predictive factors still significantly influence the overall survival despite multimodal treatment options and for superior results compared to the natural course of the disease. Furthermore, the comorbidity and side effects of the current systemic and surgical treatment modalities are not shown in most of the studies. They affect essential the patients quality of life in his remainig days and shoud be more taken in consideration before indicating surgical resection at advanced tumor stages.

Keywords

Adenocarcinoma of the pancreatic head, Significance of surgical therapy

Introduction

For most patients ductal pancreatic cancer type is refractory to most treatments and the general 5-year survival rate for all patients approached 1-12% depending on tumor stage [1-7]. The survival improvements are modest and attributed to more radical operation procedures and systemic therapies [5,8-10]. In absence of metastatic disease surgery offers the chance of improved 5 year survival after curative resection with 3% mortality in high volume centers [4,9,10]. Correct preoperative staging and the comorbidity of the patients have major influence for the indication of tumor

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resection and the outcome after resection. In the last years extended surgical resection like arterial and venous resection or the "TriangleOperation“ showed in some patients promising results, but the procedure and the outcome is still under debate [8-11]. Furthermore in most studies the anatomic localization of the tumor may have prognostic impact but this feature will not take in account in most of the studies [12-14].

Therefore the presentation of real world data from a pancreas center of excellence for carcinoma treatment may help to define the significance and status of surgical resection in the therapy of adenocarcinoma of the pancreas head.

Methods

167 patients underwent in our center resection of the pancreatic head by classic Whipple or pylorus preserving Whipple procedure between August 2014 and July 2023 in curative intention. 120 (72.3%) patients received concomittant systemic chemotherapy. Exclusion citeria were other histological types than adenocarcinoma of the pancreas, secondary tumors, bile duct carcinomas or previous pancreas surgery. Follow-up and data collection was finished in July 2023. Patients demographics and clinical characteristics were

Table 1: Patients demographics and clinical characteristics.

Characteristic	Frequency	Percentage
Number of patients	167	100
Median Age (years) (Range)	70 (42-91)	
Gender		
Male	90	53.9
Female	77	46.1
AJCC TNM stage		
IA	3	1.8
IB	1	0.6
IIA	8	4.8
IIB	9	5.4
III	141	84.4
IV	5	3
T-stage		
pT1	10	6.1
pT2	53	32.1
pT3	70	42.4
pT4	0	0
ypT1c	9	5.5
ypT2	15	9.1
ypT3	8	4.8
N-stage		
pN0	25	15
pN1	66	39.5
pN2	44	26.3
ypN0	11	6.6
ypN1	14	8.4
ypN2	7	4.2
M-stage		
M0	156	93.4
M1	11	6.6
R-stage		
R0	111	66.5
R1	54	32.3
Rx	2	1.2
CRM- resection margin		
CRM negative	75	44.9
CRM positive	92	55.1
Vascular invasion		
Yes	69	41.3
No	98	58.7
Lymphatic vessel invasion		
Yes	108	65.1
No	59	34.9
Perineural sheath infiltration		
Yes	124	74.3
No	43	25.7
Tumor size (cm), (median)	3 (0-6)	
Type of systemic treatment		
Neoadjuvant	29	17.4
Perioperative	9	5.4
Adjuvant	64	38.3
Additiv	19	11.4
No treatment	46	27.5
Response to neoadjuvant treatment (Evans-classification) n = 24 pat.		
Evans I	13	54.2
Evans IIa	3	12.5
Evans IIb	3	12.5
Evans III	5	20.8
Type of surgery		
Classic Whipple	62	37.1
Pylorus-preserving Whipple	105	62.9
Postoperative complications		
Surgical	41	24.6
Not surgical	28	16.8
Mortality		
Hospital	10	6
Outside hospital	103	62
Cause of death		
Tumor-related	93	82.3
Not tumor-related	20	17.7

Tumor progression		
All	97	58.1
Locally	40	41.2
Liver	20	20.6
Lung	9	9.3
Liver and lung	2	2.1
Locally and liver	12	12.4
Locally and lung	8	8.2
Locally and retroperitoneal	2	2.0
Locally, liver and lung	4	4.1

shown in Table 1.

After surgery all specimens underwent histopathological review and were classified according to the TNM-system. Tumor grading, circumferential resection margin (CMR), resection margin involvement (R-status), resected and involved lymphnodes, arterial and/or venous vessel involvement, infiltration of the perineural sheath and lymphatic vessel invasion were analyzed. Tumor progression and tumor relapse were diagnosed as clinical and radiological evidence at the date of new tumor mass in lymphnodes, liver, lung or locally at the resection side with detoriation of the general condition.

For statistical analysis continous variables were summarized using median and range. All data were prolectively collected and retrospectively analyzed. Categorical variables were summarized using frequency and percentage. Patients who were alive at last follow-up were censored at date of last follow-up. The median OS was estimated using the Kaplan-Meier method. For differences in survival curves the log-rank test was used, uni- and multivariable anlyses were performed using the Cox proportional hazard model. For multivariable analysis, variable selection was performed using a forward selection procedure. The proportional hazard assumption was tested on the final multivariable model using a test basing on Schoenfeld residuals. A P-value of less than 0.05 was taken as statistically significant in the univariate analyses. For the forward selection, a P-value of less than 0.1 was used for addition of variables into the multivariate model. P-values for Cox models were calculated using the likelihood ratio test.

Results

167 patients with adenocarcinoma of the pancreas head with an median age of 70 years, 53.9% male and 46.1% female, were resected between August 2014 and June 2023 by Whipple operation (37.1%) or pylorus-preserving pancreaticoduodenectomy (62.9%). In average 36 (7-83) lymph nodes were removed, about what in average 3 lymph nodes (0-43) showed infiltration of tumor. 66.5% of the patients underwent curative resection and 71.3% received concomittant systemic treatment. Most of them received adjuvant treatment (38.3%), 17.4% only neoadjuvant therapy and 5.4% perioperative chemotherapy. 68% of the patients died during the observation time, 6% was the hospital mortality, whereas in over 80% the death was tumor-related. The median time to tumor progression was 6.4 months and was diagnosed in 43% at 12 months and in 74% at 24 months.

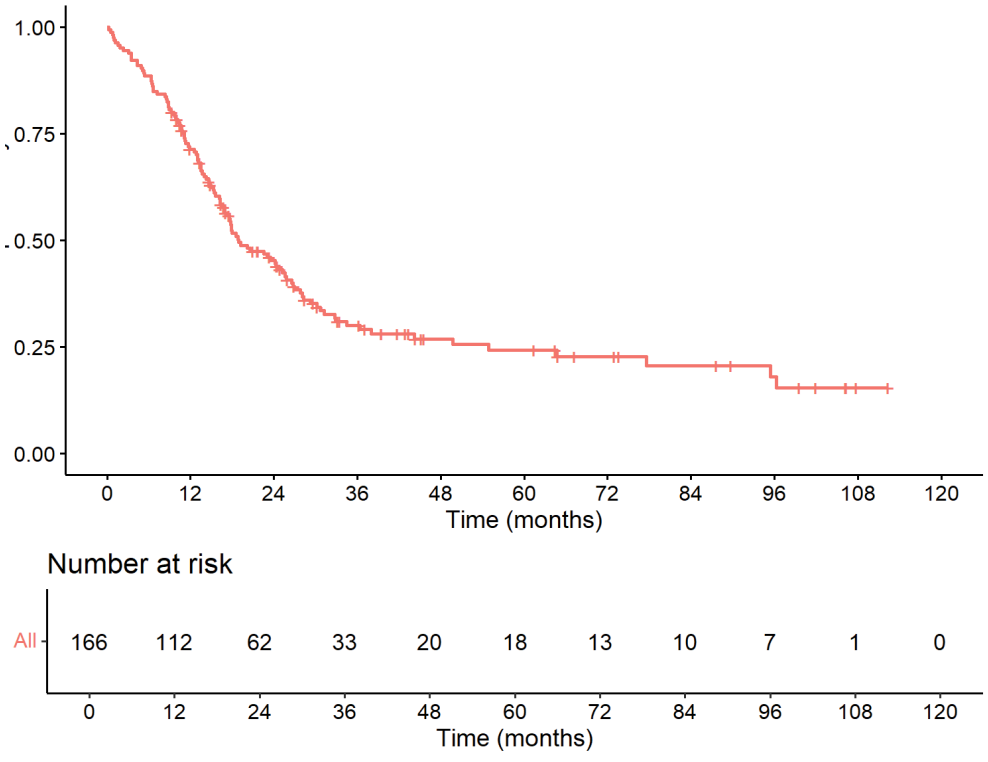

Figure 1: Overall Survival, Patients with Adenocarcinoma of the pancreas head.

The 5-year OS was 10.1% and the 1-year survival was 67.4% for all patients with surgical resection, respectively 6.7% and 72.5% for patients with systemic therapy and resection. The most common side of recurrence was located in the operation field (67.2%), distant metastases were found in the liver (26.8%) and in 23.7% in the lung. Patient demographic and clinicopathological results of the study are detailed described in Table 1.

The multivariable model revealed significant results for negative predictores in overall survival for pN-stage ($p < 0.00013$), positive resection margin (CRM)-status ($p < 0.00048$), tumor stage ($p < 0.0015$), lymphatic vessel invasion ($p < 0.0027$), R-stage ($p < 0.0055$), distant metastasis ($p < 0.0093$), vascular infiltration ($p < 0.011$) and resection of the vena mesenterica ($p < 0.025$).

The OS for all patients is shown in Figure 1, the results of all significant predictors influenzing OS were presented in Figure 2, Figure 3, Figure 4, Figure 5 and Figure 6.

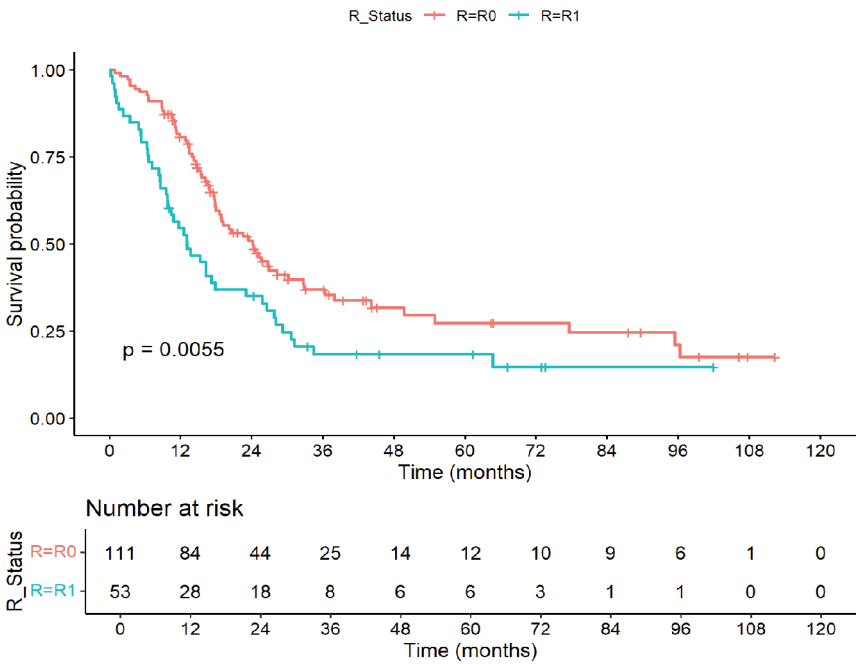

Figure 2: Survival and R-stage.

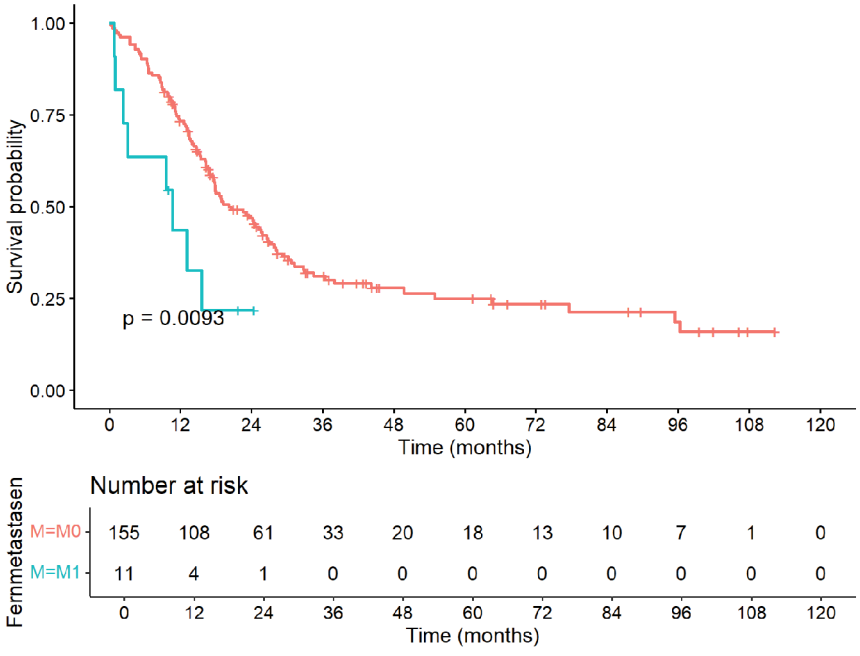

Figure 3: Overall survival and distant metatasis.

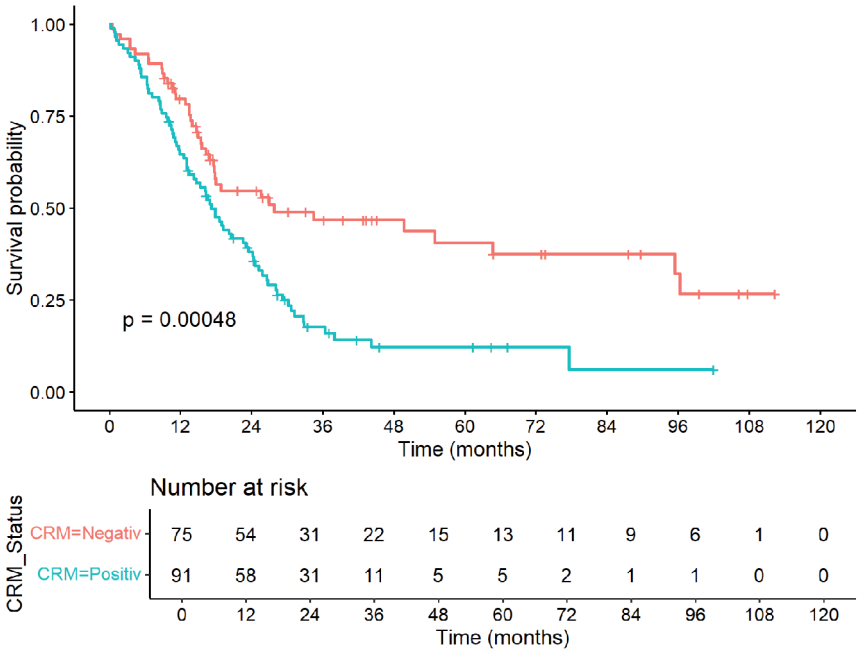

Figure 4: Overall survival and resection margin CRM.

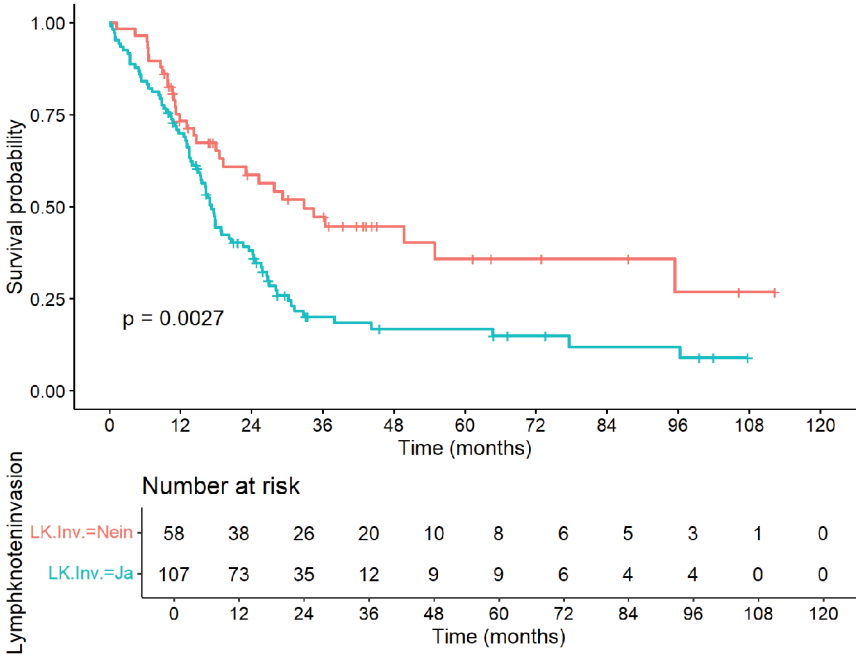

Figure 5: Overall survival and lymphatic vessel invasion.

Discussion

In this analysis of a heteregenous patient population with PHAC the median survival was 19.4 months and the 5-years survival was 10.7%. That is comparable to the results of most of the specialized centers in Western countries showing OS from 12 to 25 months and 5 year-survival rates between 3% and 28% after surgery [1,4,5,13,15,16]. 71.3% of all patients received any form of systemic treatment without any significant influence on patients OS. There seems to be a short-time effect, but no favourable significant influence on longer survival or patients quality of life.

The pattern of recurence in our study is similar to the reported literature, whereas 67.3% were found in region of the operation field [17]. Local predictive factors for radical surgery like pN-stage ($p < 0.00013$), positive resection margin (CRM)-status ($p < 0.00048$), tumor stage ($p < 0.0015$), lymphatic vessel invasion ($p < 0.0027$), R-stage ($p < 0.0055$), distant metastasis ($p < 0.0093$), vascular infiltration ($p < 0.011$)

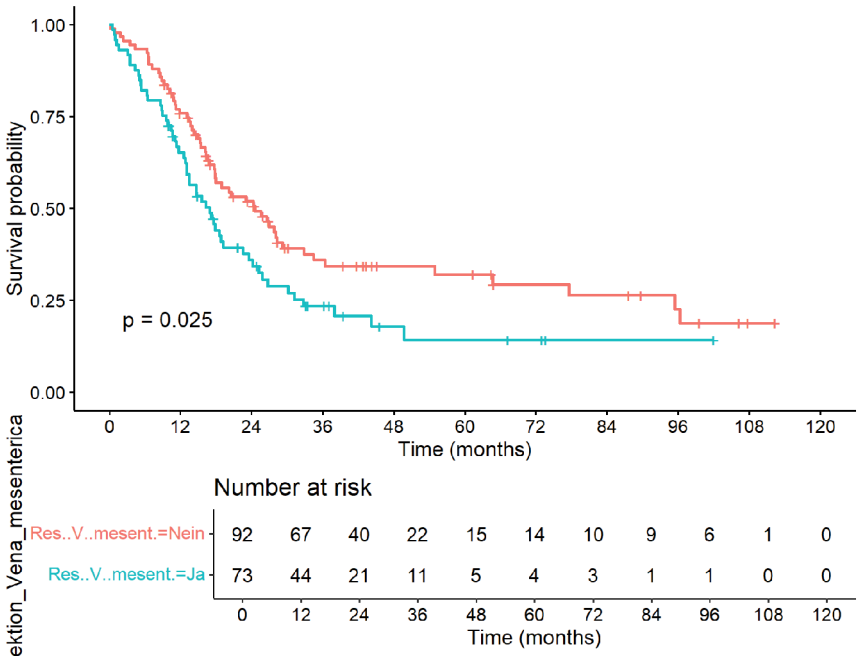

Figure 6: Overall survival and infiltration of the mesenteric vein.

and resection of the vena mesenterica ($p < 0.025$) could be influenced by the surgeon, but the results are disappointing [1,5,8,16,18].

Patients with recurrence of PHAC the OS is around 8% [19]. The group of patients with pancreatic head cancer showed in this study higher rates of local recurrence than those with body and tail cancer. Aside from that the rate of local recurrence was the highest in the region of the hepatoduodenal ligament/common hepatic artery [19]. The anatomic location of pancreatic cancer as prognostic factor is still under debate [12-14,20].

Several robust randomized control trials suggests no difference in survival of patients with PHAC between standard and extended lymphadenectomy [21]. In contrast lymphatic vessel invasion represents a decisive factor of tumor recurrence and poor survival, even in early stage patients [16].

Our results showed like those from several other studies strong limitations for patient´s survival. Even the short time of 6 months of clinical and radiological signs of tumor progression like in many other analyses prove the short-time effect of surgery in PHAC surgery [2,11,22]. That raise the question of patients benefits and high perioperative expense resulting in poor outcomes and quality of life for these patients.

Systemic therapy offers the possibility for more radical tumor removal after neoadjuvant therapy and to ensure the sucess of locally radical resection with adjuvant therapy [4,10,12]. Of interest may be the question to resect the mesenteric vein, that should increase the local radicality of tumor removal. Our results similar as many other studies showed no survival benefit from resection of the mesenteric vein, but in general patients with infiltration of the vein present higher tumor stages [23,24]. The benefit of locally radical and vessel-orientated pancreatic surgery in PHAC patients should be evaluated against enhanced postoperative complications, detoriation of quality of life and gained lifetime [6,8,9,14]. In all concepts of locally more radical surgery for PAHC patients you should never forget that it is a matter of systemic disease with an unfavourable location of the primary tumor for surgical resection. For exact examination and determination for pathohistological prognostic factors found at the specimen from patients with PHAC, standardized protocols and experienced pathologists are necessary to prove the quality of adequate surgical therapy and to optimize future treatment strategies [17,22].

In conclusion, the survival data of European patients with resectable PHAC who received similar therapies is comparable to reported randomized trials [1,6,11,13]. Maximum 20% of PHAC patients were diagnosed with localized resectable disease. Therefore surgical therapy in stage III PHAC patients despite great efforts remains always palliative proving what five-year survival rates are still 5% to 10% with low quality of life [5,8,10,12,13]. In comparison to that the natural course of disease, for all patients with the diagnose of pancreatic cancer the 5-year showed survival rates about 12% [1,4,6,12].

So far data on quality of life for patients with PAHC are not or insufficient available and should be as well part of interdisciplinary multimodal therapy decision concepts as radical surgery and/or systemic therapies. Moreover, it remains a skill and requires much experience to make the right indication for operation in PAHC patients and not to serve the surgeons enjoyment.

Conflict of Interest Statement

None declared.

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