A simple prognostic score to predict recurrence after pancreaticoduodenectomy for ampullary carcinoma: results from the French prospective FFCD-AC cohort

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Highlights

- **FFCD-AC is a French nationwide prospective cohort of 370 patients resected by pancreatoduodenectomy for a AC.**
- **2-year disease-free survival was 62%, aligned with previous cohorts and 61% of patients received adjuvant therapy.**
- **FFCD-AC proposes a user-friendly score to predict recurrence based on tumor subtype, grade and stage.**
- **After propensity score, FFCD-AC suggests that adjuvant therapy is associated with improved survival outcomes.**

Introduction

Ampullary carcinoma (AC) is a rare disease accounting for 0.2% of gastrointestinal cancers and corresponding to a heterogeneous group of cancers divided into 3 subtypes with different morphological patterns and prognostic profiles, as follows: intestinal (30-40% of cases), pancreatobiliary (45-60%) and mixed, also sometimes called undetermined (10-20%). In resected patients, recurrence rate is high with 2-year disease-free survival (DFS) rates ranging from 50% to 66.2%.[1] However, the place of adjuvant therapy after curative-intent resection is still debated as no standard of care has been fully established so far. Here we propose an integrated score based on routine post-operative pathological parameters such as tumor stage, tumor grade and pathological subtype to easily estimate the risk of recurrence and to help decision-making regarding adjuvant treatment.

Patients and method

Study design and patient selection

The FFCD-AC cohort is a prospective French cohort of patients surgically resected for an AC. In this study, only patients resected by pancreaticoduodenectomy (PD) were eligible.

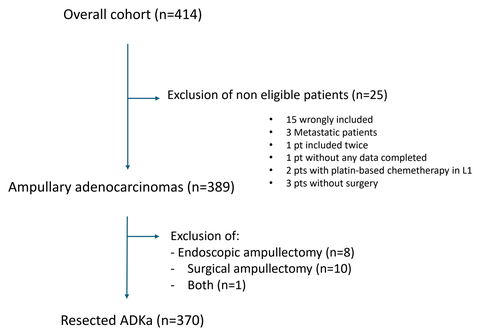
Inclusion criteria: aged 18 and over, resection for a non-metastatic AC without macroscopic residual tumor residue (R2) within 1 year before inclusion.
Non-inclusion criteria: non-ampullary tumors, ampullary tumors other than adenocarcinoma, metastatic or unresectable locally advanced AC at diagnosis..

Study objectives

The primary objective of this study was to describe prognostic factors associated with DFS after PD so as to propose a user-friendly score to better estimate the risk of disease recurrence. Secondary objectives were the relation between these prognostic factors and OS, and to evaluate the impact of adjuvant therapy on survival outcomes.

Results

Patients' selection and characteristics



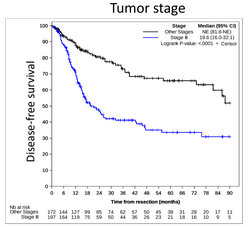
Patients' characteristics	Overall cohort (n=370)
Age, median (Min-Max)	68.5 (32.0-87.0)
Sex	
Male	199 (53.8%)
Female	171 (46.2%)
ECOG performance status, n=321	
0	180 (56.1%)
1	120 (37.4%)
2	21 (6.5%)
Body Mass Index (kg/m²), n=367 median (IQR*)	29.5 (26.2 ; 33.7)
pTNM Stage	
0	7 (1.9%)
I	100 (27.1%)
II	65 (17.6%)
III	197 (53.4%)
Resection margin, n=369	
R0	359 (97.3%)
R1	10 (2.7%)
Pathological subtype, n=370	
Intestinal	109 (29.5%)
Pancreatobiliary	150 (40.5%)
Mixed/Undetermined	32 (8.6%)/79 (21.4%)
Not determined	79 (21.4%)
Tumor grade	
Low	103 (27.8%)
Intermediate	166 (44.9%)
High	44 (11.9%)
Undetermined	57 (15.4%)
Adjuvant chemotherapy, n=370	
No	144 (38.9%)
Yes	226 (61.1%)
Single-agent	73 (32.3%)
Doublet/triplet	153 (67.7%)

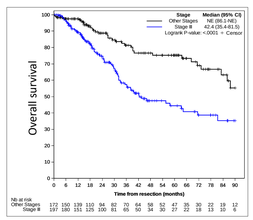
Prognostic factors influencing survival outcomes

	Disease-free survival				Overall survival			
	Univariable analysis		Mutivariable analysis		Univariable analysis		Mutivariable analysis	
	HR [CI 95%]	P	HR [CI 95%]	P	HR [CI 95%]	P	HR [CI 95%]	P
Age (years)								
< 75	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
≥ 75	1.42 [1;2.02]	0.048	1.20 [0.79;1.82]	0.395	1.69 [1.14;2.51]	0.009	1.66 [1.03;2.66]	0.036
ECOG PS								
0	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
≥ 1	1.56 [1.1;2.22]	0.013	1.45 [0.98;2.14]	0.066	1.48 [0.98;2.23]	0.059	1.20 [0.76;1.91]	0.438
TNM Stage								
0-I-II	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
III	2.63 [1.9;3.8]	<0.0001	2.86 [1.89 ;4.17]	<0.0001	2.44 [1.6;3.7]	<0.0001	2.63 [1.67;4.17]	<0.0001
Tumor grade								
Low	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Intermediate	1.49 [0.97 ;2.3]	0.067	1.24 [0.78 ;1.99]	0.368	1.55 [0.94 ;2.56]	0.084	1.41 [0.81 ;2.45]	0.224
High	2.50 [1.46 ;4.29]	0.001	2.51 [1.42 ;4.43]	0.002	2.79 [1.53 ;5.09]	0.001	2.81 [1.48 ;5.32]	0.002
Undetermined	2.11 [1.27 ;3.52]	0.004	1.95 [1.09 ;3.5]	0.025	1.73 [0.92 ;3.23]	0.087	1.62 [0.77 ;3.37]	0.202
Pathological subtype								
Intestinal	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Non-intestinal	2.14 [1.42 ;3.22]	<0.001	1.58 [1 ;2.49]	0.052	1.99 [1.24 ;3.19]	0.005	1.38 [0.81 ;2.33]	0.234

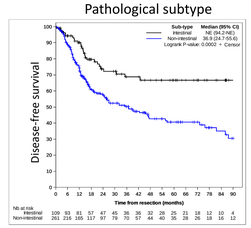
Survival outcomes according to tumor stage, pathological subtype and tumor grade in univariable analyses:

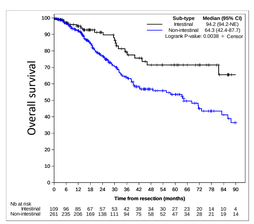
Tumor stage



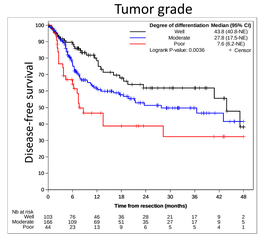


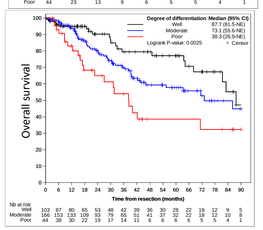
Pathological subtype





Tumor grade

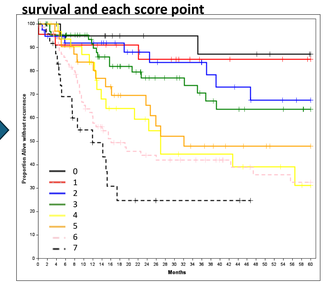




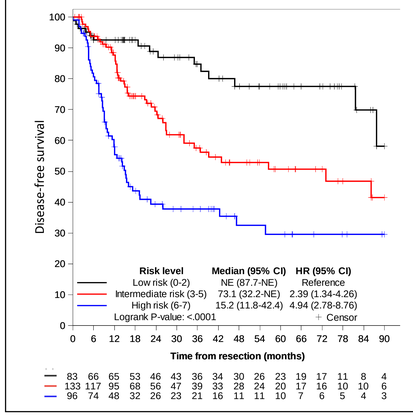
Prognostication score construction

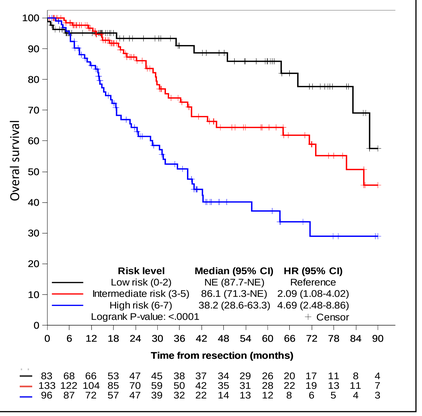
Variables		Coefficient of variable in multivariable analysis mDFS (n=312)	Score weighting
Tumor stage	Stage I-II	Ref	0
	Stage III	2.507	3
Tumor grade	Low	Ref	0
	Intermediate	1.275	1
	High	2.281	2
Tumor subtype	Intestinal	Ref	0
	Non-intestinal	2.057	2

Relationship between progression-free survival and each score point



Disease-free survival and overall survival according to score class





Disease-free survival and overall survival according to different risk level groups and the presence of adjuvant therapy or not in univariable analyses.

	Disease-free survival			Overall survival		
Risk level	Low (n=83)	Intermediate (n=133)	High (n=96)	Low (n=83)	Intermediate (n=133)	High (n=96)
Median [95%CI] (months)	NR [81.6;NR]	73.1 [32.1;NR]	15.2 [11.3;22.6]	NR [83.1;NR]	86.1 [64. 3;NR]	38.2 [28.2;55.6]
HR [IC 95%]	Ref	2.39 [1.34;4.26]	4.94 [2.78;8.76]	Ref	2.09 [1.08;4.02]	4.69 [2.48;8.86]
P		0.003	<0.0001		0.03	<0.0001
Post-operative strategy						
Surveillance						
N	55	37	21	55	37	21
Median [95%CI] (months)	NR [87.69;NR]	39.26 [13.86;NR]	6.34 [4.47;9.92]	NR [87.69;NR]	64.26 [26.94;NR]	20.07 [7.39;39.95]
Adjuvant chemotherapy	28	96	75	28	96	75
N	81.58	86.14	19.12	83.12	86.14	39.49
Median [95%CI] (months)	[46.78;NR]	[32.13;NR]	[14.06;47.34]	[63.61;NR]	[71.26;NA]	[28.16;71.43]

Conclusion

- This study proposes a user-friendly score based on tumor subtype, tumor grade and TNM stage, dividing patients in low, intermediate and high-risk levels, linearly correlated with significant decreases in DFS and OS.
- After propensity score matching, this study suggests that adjuvant therapy is associated with longer survival outcomes.
- External validation dataset would be interesting to confirm these 3 parameters, our results suggest to stratify future adjuvant trials on these 3 important parameters as it has been agreed on for the FFCD 2105 / PRODIGE 98 – AMPIRINOX trial.

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