

## 2016 Pancreatic Cancer: Global view

# Re-evaluation of classical prognostic factors in resectable ductal adenocarcinoma of the pancreas

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reported incidence rates. Surgical resection offers the only potential cure. Yet, even among patients that undergo tumor resection, recurrence rates are high and long-term survival is scarce. Various tumor-related factors have been identified as predictors of survival after potentially curative resection. These factors include tumor size, lymph node disease, tumor grade, vascular invasion, perineural invasion and surgical resection margin. This article will re-evaluate the importance of these factors based on recent publications on the topic, with potential implications for treatment and outcome in patients with pancreatic cancer.

**Key words:** Pancreatic cancer; Survival; Prognostic factors

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**Core tip:** Many studies have investigated morphological indicators of survival in patients with resectable pancreatic cancer. This article scrutinizes the recent literature related to these classical prognostic factors and examines whether these factors still are able to influence patients' outcomes in the era of multimodal treatment.

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## Abstract

Pancreatic ductal adenocarcinoma carries a poor prognosis with annual deaths almost matching the

## INTRODUCTION

Pancreatic cancer has a devastatingly poor prognosis.

The overall survival remains unchanged over a wide period of time with at a 5-year survival of 5%-10%<sup>[1]</sup>. Furthermore, according to recent data, the incidence of pancreatic cancer is increasing<sup>[2-4]</sup>. Pancreatic ductal adenocarcinoma constitutes the most common histopathological subtype of pancreatic cancer originating from the ductal cells of the exocrine pancreas. Surgery remains the only cure for pancreatic cancer, but long-term survival is uncommon despite the addition of oncological treatments.

Over the years, several important prognostic factors for resectable pancreatic cancer have been identified. Among these prognostic factors are tumor size, presence or absence of lymph node metastases (loco-regional and/or distant), vascular tumor involvement (e.g., portal vein, mesenteric vein and/or artery), perineural tumor growth and resection margin status (from tumor to resection line)<sup>[5-9]</sup>.

Many studies have been conducted to elucidate the relative importance of these prognostic factors in terms of recurrence-free survival and long-term cure. Despite this information, limited progress has been made regarding survival aspects. Pancreatic surgery is associated with high morbidity and potentially also immune suppression. Therefore, it is of vital importance to accurately determine which patients that really derive benefit from surgery in order to avoid unnecessary surgical intervention, as well as facilitate treatment planning and guide neo- and adjuvant treatments. The aim of this review was to re-investigate classical morphological prognostic factors in resectable pancreatic cancer by summarizing the recent literature on the topic published since the year 2000.

## TUMOR SIZE

Tumor size is a morphological variable that can be determined preoperatively and as such carries much important information for treatment planning. Being part of the current TNM staging system of pancreatic cancer, tumor size is the only discriminant between T1 and T2 tumors (cut-off 2 cm). However, the size at which point a pancreatic tumor becomes associated with aggressive features remains undetermined. This is why most studies that have evaluated the effects of tumor size on survival have not used uniform definitions (Table 1). In general, larger tumors > 2-3 cm have worse prognosis compared to smaller tumors. Tumor size has also been linked to other adverse prognostic factors. For example, tumors with a diameter above 2 cm have been found to have an increased risk of lymph node metastases<sup>[10]</sup>.

Tumor size may also affect the rates of margin positivity following pancreatic surgery. It has been found that larger tumors increase the risk of tumor deposits being harbored in the resection line<sup>[11]</sup>. Larger tumors generally have a greater malignant potential, increasing the risk of tumor involvement of

peripancreatic structures<sup>[12,13]</sup>.

However, although most studies indicate impaired survival for larger tumors, a small tumor diameter does not exclude poor prognosis<sup>[14,15]</sup>. Interestingly, it has been found that tumors with a diameter less than 1 cm may also be associated with malignant potential and rapid disease progression<sup>[16,17]</sup>. Histopathological data obtained from analysis of "early" pancreatic cancer show that small tumor may display the same microvascular invasiveness pattern (*i.e.*, a poor prognostic factor) as larger tumors<sup>[18,19]</sup>.

This, somewhat, unclear relationship between tumor size and prognosis may reflect different tumor biology and invasiveness, independent of tumor size<sup>[20]</sup>, regulating outcome.

## LYMPH NODE STATUS

Dissemination into the lymphatic system is a major route for pancreatic cancer metastasis. Lymph node status has been demonstrated to be one of the most potent predictors of survival. Several recent studies (Table 2) have proposed that the ratio of metastatic to examined lymph nodes (LNR) may be more powerful predictors of survival than the mere dichotomization into positive or negative lymph nodes. LNR also seems to have negative impact on the long-term survival ( $\geq 60$  mo)<sup>[21]</sup>. Poor prognosis has been observed with an LNR over 0.3-0.4.

There is a wide time span in terms of median survival between studies evaluating the impact of lymph node status on survival after resection for pancreatic cancer. Patients with N0 tumors displayed a superior median survival of up to 40 mo and patients with LNR > 0.3 displayed a median survival of 6 mo at the lowest. The wide range in median survival may reflect different biology in those tumors that spread to lymph nodes and those that do not. It may also be speculated that there is a biological difference in the tumor invasiveness both regarding loco-regional and distant lymph node metastases. In general, lymph node metastases can be correlated to increasing tumor size but not in all of the cases.

It is recommended to sample at least 12 lymph nodes for histopathological diagnosis and staging<sup>[22]</sup>. Standard lymphadenectomy for pancreatic head tumors include resection of lymph node stations 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a and 17b, while tumors of the body and tail of the pancreas require removal of stations 10, 11, and 18. Extended lymphadenectomy during Whipple's procedure include resection of lymph nodes along the left side of the superior mesenteric artery and around the celiac trunk, splenic artery or left gastric artery. There is no convincing evidence that extensive lymph node resection in conjunction to pancreatic surgery increases the overall survival and is therefore not recommended<sup>[23]</sup>.

Lymph node status may also be defined based

**Table 1** Tumor size and survival for resectable pancreatic cancer

Ref.	Year	n	Tumor size, cut-off	Median OS	Statistical model	HR (95%CI)	P value
Matsumoto <i>et al</i> <sup>[38]</sup>	2015	968	≥ 3 cm	NR	Multivariable	1.72 (1.16-2.56)	0.006
Jeong <i>et al</i> <sup>[39]</sup>	2015	276	≤ 2.5 cm	13 mo	Multivariable	1.65 (1.17-2.32)	0.004
			> 2.5 cm	25 mo			
Hur <i>et al</i> <sup>[17]</sup>	2015	18338	<i>In situ</i>	120 mo	Multivariable	1	
			≤ 1.0 cm	27 mo		3.09 (2.35-4.07)	< 0.001
			1.1-2.0 cm	17 mo		4.35 (3.42-5.53)	< 0.001
			> 2.0 cm	11 mo		5.69 (4.49-7.21)	< 0.001
Yamamoto <i>et al</i> <sup>[40]</sup>	2015	195	≤ 2 cm	29 mo (mean)	Multivariable	0.40 (0.17-0.83)	0.012
Elberm <i>et al</i> <sup>[41]</sup>	2015	1070	< 2 cm	19 mo	Multivariable	0.63 (0.50-0.78)	< 0.001
Liu <i>et al</i> <sup>[31]</sup>	2015	411	> 2 cm	NR	Univariable	1.46 (1.14-1.88)	0.003
Okada <i>et al</i> <sup>[42]</sup>	2014	200	≥ 3 cm	NR	Multivariable	3.26 (1.52-7.00)	0.002
Dusch <i>et al</i> <sup>[21]</sup>	2014	415	< 3 cm	16 mo	Univariable	-	< 0.03
Shin <i>et al</i> <sup>[15]</sup>	2014	537	≤ 3 cm	22 mo	Multivariable	1.4 (1.13-1.73)	0.002
			> 3 cm	14 mo			
Kooby <i>et al</i> <sup>[37]</sup>	2014	1399	Continuous	20 mo	Multivariable	1.12 (1.06-1.18)	< 0.001
Petermann <i>et al</i> <sup>[10]</sup>	2013	114	≤ 2 cm	35 mo	Multivariable	0.52 (0.25-1.05)	0.071
			2.1-3.4 cm	16 mo			
			3.5-4.5 cm	20 mo			
			> 4.5 cm	8 mo			
Jamieson <i>et al</i> <sup>[43]</sup>	2013	217	≤ 3 cm	23 mo	Multivariable	1.28 (0.93-1.76)	0.13
			> 3 cm	16 mo			
Franko <i>et al</i> <sup>[14]</sup>	2013	7135	≤ 1 cm	N0/N1: 38/18 mo	Multivariable	1	
			1.1-2 cm	N0/N1: 26/19 mo		1.18 (0.94-1.48)	0.152
			> 2 cm	N0/N1: 19/14 mo		1.67 (1.34-2.07)	< 0.001
Lad <i>et al</i> <sup>[44]</sup>	2013	382	Continuous	16 mo	Multivariable	1.23 (1.07-1.41)	0.003
Sugiura <i>et al</i> <sup>[45]</sup>	2013	208	≥ 3 cm	NR	Univariable	NR	0.014
Hong <i>et al</i> <sup>[18]</sup>	2012	209	< 3 cm	20 mo	Univariable	NR	0.06
			≥ 3 cm	15 mo			
Bhatti <i>et al</i> <sup>[46]</sup>	2010	84	≤ 2 cm	34 mo	Univariable	NR	0.017
			> 2 cm, invasion-	27 mo			
			> 2 cm, invasion+	11 mo			
Yamada <i>et al</i> <sup>[47]</sup>	2009	335	> 4 cm	NR	Multivariable	2.69 (1.30-5.56)	< 0.05
Ueda <i>et al</i> <sup>[48]</sup>	2009	140	< 3 cm	22 mo	Multivariable	1.85 (1.14-3.10)	0.013
			≥ 3 cm	11 mo			
Kaneoka <i>et al</i> <sup>[49]</sup>	2009	84	< 2 cm	NR	Multivariable	1	
			2-4 cm	20 mo		1.7 (1.0-3.1)	0.031
			> 4 cm	11 mo		2.3 (1.3-4.5)	0.003
Campbell <i>et al</i> <sup>[50]</sup>	2009	163	Continuous	14 mo	Multivariable	1.02 (1.00-1.03)	0.049
Doi <i>et al</i> <sup>[51]</sup>	2007	133	≤ 4 cm	45% dead within 1 yr	Univariable	1.55 (1.06-2.24)	0.02
			> 4 cm	67% dead within 1 yr			
Zacharias <i>et al</i> <sup>[52]</sup>	2007	81	≤ 3 cm	28 mo	Multivariable	1.9 (1.1-3.1)	0.018
			> 3 cm	14 mo			
Pawlik <i>et al</i> <sup>[6]</sup>	2007	905	≥ 2 cm	17 mo	Multivariable	1.24 (1.01-0.51)	0.04
Moon <i>et al</i> <sup>[53]</sup>	2006	94	< 3 cm	25 mo	Multivariable	0.46 (0.27-0.78)	0.004
Cleary <i>et al</i> <sup>[20]</sup>	2004	123	Continuous	14 mo	Univariable	1.2 (1.0-1.4)	0.01
Ahmad <i>et al</i> <sup>[54]</sup>	2001	125	< 2 cm	16 mo	Univariable	1	
			2-4 cm			1.05 (0.58-1.89)	0.87
			> 4 cm			1.15 (0.61-2.15)	0.66
Sohn <i>et al</i> <sup>[55]</sup>	2000	616	< 3 cm	21 mo	Multivariable	0.72 (0.57-0.90)	0.004
			≥ 3 cm	14 mo			
Meyer <i>et al</i> <sup>[56]</sup>	2000	113	≤ 2 cm	28 mo	Multivariable	2.27	< 0.006
			> 2 cm	13 mo			

OS: Overall survival.

on the location of the lymph nodes involved. Several studies describe lymph node involvement as N1 (metastases in loco-regional lymph nodes) or N2-3 (metastases in distant lymph nodes). A few studies evaluated para-aortic lymph denoted as N3. There is a clear survival difference between local or distant lymph nodes metastases (*e.g.*, para-aortic lymph node metastases). Most studies, but not all, report

that para-aortic lymph node involvement is associated with a poor prognosis, being an independent factor of adverse outcome (Table 3). Frozen-section examination of para-aortic nodes accurately detects distant lymphatic involvement reliably and should be routinely performed<sup>[24]</sup>. The presence of metastases is considered a contraindication to proceed with pancreatic resection.

**Table 2** Prognostic relevance of lymph node ratio

Ref.	Year	n	Cut-off	Detection rate (%)	Median OS with highest LNR (mo)	Survival model	HR (95%CI)	P value
Fouquet <i>et al</i> <sup>[34]</sup>	2014	166	0.2	76 (46)	NR	Multivariable	2.38 (1.4-4.0)	0.001
Dusch <i>et al</i> <sup>[21]</sup>	2014	415	Continuous	0.10 (0-0.81) <sup>1</sup>	NR	Multivariable	1.73 (NR)	0.002
Valsangkar <i>et al</i> <sup>[57]</sup>	2013	14907	0.3	4038 (27)	NR	Multivariable	2.27 (1.67-3.08)	< 0.001
Lewis <i>et al</i> <sup>[58]</sup>	2013	424	0.3	83 (20)	16	Multivariable	1.97 (NR)	< 0.001
Robinson <i>et al</i> <sup>[59]</sup>	2012	131	0.15	70 (53)	NR	Multivariable	4.14 (NR)	< 0.010
La Torre <i>et al</i> <sup>[60]</sup>	2011	101	0.2	30 (30)	13	Multivariable	4.88 (1.07-22.2)	0.008
Bhatti <i>et al</i> <sup>[46]</sup>	2010	84	0.3	26 (31)	6	Multivariable	2.7 (1.6-4.4)	0.010
Riediger <i>et al</i> <sup>[61]</sup>	2009	182	0.3	32 (18)	NR	Multivariable	2.2 (1.4-3.6)	< 0.001
Slidell <i>et al</i> <sup>[22]</sup>	2008	3868	0.4	602 (16)	10	Multivariable	1.82 (1.59-2.07)	< 0.001
Pawlik <i>et al</i> <sup>[6]</sup>	2007	905	0.4	154 (17)	12	Multivariable	2.55 (1.75-2.70)	0.001

<sup>1</sup>Mean (range). LNR: Lymph node ratio; OS: Overall survival.**Table 3** Para-aortic lymph node involvement and survival

Ref.	Year	n	Detection rate (%)	Median OS with PALN (mo)	Survival model	HR (95%CI)	P value
Sho <i>et al</i> <sup>[62]</sup>	2015	882	102 (12)	17	Multivariable	1.15 (0.87-1.50)	0.335
Schwarz <i>et al</i> <sup>[24]</sup>	2014	111	17 (15)	16	Univariable	NR	0.038
Kanda <i>et al</i> <sup>[63]</sup>	2011	429	49 (11)	8	Univariable	NR	0.006
Murakami <i>et al</i> <sup>[64]</sup>	2010	103	18 (17)	12	Multivariable	1.84 (0.28-1.07)	0.078
Doi <i>et al</i> <sup>[51]</sup>	2007	133	19 (14)	5	Multivariable	2.90 (1.60-5.02)	0.001
Shimada <i>et al</i> <sup>[65]</sup>	2006	133	29 (22)	13	Univariable	NR	< 0.001

OS: Overall survival; PALN: Para-aortic lymph node involvement.

## TUMOR GRADE

The WHO classification of tumor grade in pancreatic cancer is based on the original proposal of Klöppel *et al*<sup>[25]</sup> and takes into consideration mucin production, glandular differentiation, mitotic activity and nuclear atypia. Several studies have shown that tumor grade is an important prognostic indicator after resection of pancreatic cancer<sup>[26-28]</sup>. Wasif *et al*<sup>[29]</sup> analyzed 8082 patients with resected pancreatic cancer. This study found that high tumor grade had a larger impact on survival than both tumor size and lymph node metastases, both of which are part of the current TNM staging system. This observation lead the authors to conclude that the inclusion of tumor grade into the TNM staging for pancreatic cancer would improve prognostic stratification and better reflect the aggressive prognosis of poorly differentiated tumors.

## VASCULAR INVASION AND PORTO-MESENTERIC VEIN RESECTION

Pancreatic tumors may occlude peripancreatic vascular structures, either partly or totally, and in the latter case are categorized as unresectable. The extent of vessel wall involvement, *i.e.*, involvement of tunica adventitia, media or intima, has been correlated with outcome<sup>[30]</sup>. Invasion of major retroperitoneal blood vessels has been found to be an independent predictor of poor survival<sup>[11,30,31]</sup>. Vascular resections should be performed if it is possible to obtain R0 resections,

which is supported by previous histopathological data<sup>[32]</sup>. In the situation with positive para-aortic lymph nodes, however, venous and arterial tumor involvement may not be a prognostic factor for survival. It has been speculated that para-aortic lymph node involvement might be a stronger prognostic factor than vascular involvement.

Portal vein and superior mesenteric vein invasion often occurs due to the anatomic location of the tumor. Venous invasion was for a long time considered a contraindication to surgery. Today, vascular resection has become more common. Most studies indicate that vascular resection has similar survival rates as standard resection (Table 4), but it should be performed in carefully selected cases, given the slightly increased perioperative mortality rate and some reports that indicate worse survival, likely due to more advanced disease. Arterial resection during pancreatic resection is associated with poor short- and long-term outcome and is not recommended outside of clinical trials<sup>[33]</sup>.

## PERINEURAL INVASION

Perineural invasion (PNI) is a common way of pancreatic tumor growth. Several studies have revealed that PNI in specimens from patients who underwent surgical resection was associated with worse survival (Table 5). Data also indicate that perineural involvement is a predictor for early cancer recurrence<sup>[34]</sup>. The lack of perineural involvement may be a good prognostic

**Table 4 Porto-mesenteric vein resection and survival**

Ref.	Year	n	VR rate (%)	Median OS without VR/with VR (mo)	Survival model	HR (95%CI)	P value
Jeong <i>et al</i> <sup>[39]</sup>	2015	276	46 (17)	16/12	Multivariable	1.15 (0.78–1.71)	0.474
Murakami <i>et al</i> <sup>[66]</sup>	2015	937	435 (46)	26/19	Multivariable	1.16 (0.89–1.53)	0.268
Wang <i>et al</i> <sup>[67]</sup>	2014	122	64 (53)	31/18	Multivariable	NR	NS
Kelly <i>et al</i> <sup>[68]</sup>	2013	492	70 (14)	19/12	Multivariable	1.14 (0.83–1.57)	0.410
Gong <i>et al</i> <sup>[69]</sup>	2013	566	119 (21)	20/13	Univariable	NR	< 0.050
Castleberry <i>et al</i> <sup>[70]</sup>	2012	3582	281 (8)	Increased 30-d postoperative mortality, 2.9% vs 5.7%	Multivariable	2.1 (1.22–3.73)	0.008
Chakravarty <i>et al</i> <sup>[71]</sup>	2010	87	12 (14)	10/9	Multivariable	NR	0.591
Ouaissi <i>et al</i> <sup>[72]</sup>	2010	149	59 (40)	19/18	Multivariable	DFS: 0.43 (0.22–0.82)	0.011
Kaneoka <i>et al</i> <sup>[49]</sup>	2009	84	42 (50)	26/12	Multivariable	NR	NS
Kurosaki <i>et al</i> <sup>[73]</sup>	2008	77	35 (45)	20/20	Univariable	NR	0.330
Fukuda <i>et al</i> <sup>[30]</sup>	2007	121	37 (31)	NR	Univariable	NR	0.550
Carrère <i>et al</i> <sup>[74]</sup>	2006	133	45 (34)	19/15	Univariable	NR	0.690
Shimada <i>et al</i> <sup>[75]</sup>	2006	149	86 (58)	35/14	Multivariable	2.25 (1.09–3.62)	NR
Tseng <i>et al</i> <sup>[76]</sup>	2004	291	110 (38)	27/23	Multivariable	1.13 (0.79–1.63)	0.500
Poon <i>et al</i> <sup>[77]</sup>	2004	50	12 (24)	21/20	Univariable	NR	0.769
Nakagohri <i>et al</i> <sup>[78]</sup>	2003	81	33 (41)	10/15	Univariable	NR	NS
Bachelier <i>et al</i> <sup>[79]</sup>	2001	87	31 (36)	12/12	Univariable	NR	0.480

OS: Overall survival; PALN: Para-aortic lymph node involvement; NS: Not significant.

**Table 5 Prognostic role of perineural invasion**

Ref.	Year	n	Detection rate (%)	Median OS with PNI (mo)	Survival model	HR (95%CI)	P value
Kondo <i>et al</i> <sup>[36]</sup>	2015	209	197 (94)	15	Multivariable	No of PNIs: < 14: 1 14–40: 1.96 (1.01–3.93) > 40: 5.81 (3.17–11.35)	< 0.001
Fouquet <i>et al</i> <sup>[34]</sup>	2014	166	133 (81)	NR	Multivariable	2.77 (1.40–5.26)	0.001
Chatterjee <i>et al</i> <sup>[80]</sup>	2012	212	123 (58)	29	Multivariable	1.70 (1.18–2.45)	0.005
Takahashi <i>et al</i> <sup>[81]</sup>	2012	110	56 (51)	NR	Multivariable	2.48 (1.11–5.52)	0.026
Sahin <i>et al</i> <sup>[82]</sup>	2012	544	473 (87)	29	Multivariable	1.60 (1.08–2.36)	0.019
Robinson <i>et al</i> <sup>[59]</sup>	2012	134	128 (96)	NR	Multivariable	5.52 (NR)	< 0.050
Kanda <i>et al</i> <sup>[63]</sup>	2011	429	148 (34)	NR	Multivariable	1.72 (1.15–2.58)	< 0.001
Shimada <i>et al</i> <sup>[35]</sup>	2011	153	146 (94)	7 (DFS)	Multivariable	2.19 (1.36–3.52)	0.001
Murakami <i>et al</i> <sup>[64]</sup>	2010	103	31 (30)	NR	Multivariable	1.93 (1.03–3.62)	0.041
Kazanjan <i>et al</i> <sup>[83]</sup>	2008	182	112 (62)	20	Multivariable	2.66 (1.74–4.06)	< 0.001

OS: Overall survival; PNI: Perineural invasion.

marker of disease free survival<sup>[35]</sup>. However, various criteria for the diagnosis of PNI have been used, and the frequency of PNI in pancreatic cancer varies widely among the previous reports, between 30%–96%. According to a recent study the severity of PNI can be correlated with survival<sup>[36]</sup>. This study demonstrated that the number of PNIs was a potent predictor of survival in patients with resectable pancreatic cancer.

## RESECTION MARGINS

The R classification for pancreatic cancer entails estimation of the radicality of resection. R0 denotes complete microscopic tumor removal. R1 indicates microscopic residual tumor, while R2 indicates macroscopic residual tumor. The influence of margin status on outcomes in pancreatic cancer remains controversial (Table 6). This is largely due to lack of standardization of margin definitions and reporting.

Most studies show a worsened prognosis of R1 compared to R0 resection.

The poor prognosis in R1 resections is underscored by the observation that once tumor cell deposits have reached beyond the resected pancreatic surface area, it is difficult to improve survival by trying to convert R1 to R0 resections. Data show that the overall survival of turning R1 to R0 resections is still not convincingly high and once a positive intraoperative resection margin is discovered on frozen section it is doubtful whether the conversion to R0 resection is a “true R0” since the overall survival is not changed<sup>[37]</sup>.

The definition of margin clearance is still under debate. However, nowadays most studies now use a margin clearance over 1 mm to define R1 resection.

## CONCLUSION

Despite technical advances in the field of pancreatic



Table 6 Radicality of resection and survival

Ref.	Year	n	R1 definition	R1 rate (%)	Median OS R0/R1 (mo)	Survival model	HR (95% CI)	P value
Kooby <i>et al</i> <sup>[37]</sup>	2014	1399	1 mm	R0 (86) R1→R0 (5) R1 (9)	21 12 14	Multivariable	1 1.55 (1.11-2.16) 1.46 (1.13-1.90)	0.009 0.004
Konstantinidis <i>et al</i> <sup>[84]</sup>	2013	554	1 mm	157 (28)	35/14	Univariable	NR	< 0.001
Kimbrough <i>et al</i> <sup>[85]</sup>	2013	283	0 mm	76 (27)	22/15	Multivariable	NR	NS
Gnerlich <i>et al</i> <sup>[86]</sup>	2012	285	1 mm	97 (34)	22/16	Univariable	NR	0.010
Jamieson <i>et al</i> <sup>[11]</sup>	2010	148	1 mm	110 (74)	27/15	Multivariable	1.76 (1.15-2.28)	0.009
Van den Broeck <i>et al</i> <sup>[87]</sup>	2009	144	1 mm	48 (33)	24/12	Univariable	NR	< 0.001
Chang <i>et al</i> <sup>[88]</sup>	2009	365	0 mm	131 (36)	20/13	Multivariable	1.48 (1.15-1.89)	0.002
Campbell <i>et al</i> <sup>[50]</sup>	2009	163	1 mm	128 (79)	25/13	Multivariable	1.44 (0.90-2.32)	0.132
Westgaard <i>et al</i> <sup>[89]</sup>	2008	40	1 mm	18 (45)	16/11	Univariable	NR	0.300
Esposito <i>et al</i> <sup>[90]</sup>	2008	111	1 mm	84 (76)	NR	Univariable	NR	0.370
Raut <i>et al</i> <sup>[91]</sup>	2007	360	0 mm	61 (17)	28/22	Multivariable	NR	NS
Verbeke <i>et al</i> <sup>[92]</sup>	2006	26	1 mm	22 (85)	37/11	Multivariable	NR	0.790
Howard <i>et al</i> <sup>[93]</sup>	2006	226	0 mm	68 (30)	NR	Multivariable	1.39 (1.02-1.90)	0.030

NS: Not significant; OS: Overall survival.

surgery, the long-term prognosis of pancreatic cancer still remains dismal. This article updates the role of established prognostic factors after curatively intended surgery for pancreatic cancer.

Tumor size is a prognostic factor, with survival decreasing in parallel to increased tumor size. However, small tumors (< 2 cm) may still metastasize and be associated with a poor outcome.

Lymph node involvement is associated with poor survival. A LNR of > 0.3 is a strong prognostic determinant. Para-aortic node sampling with frozen-section examination detects distant lymphatic involvement reliably and should be performed routinely. Metastatic deposits in para-aortic lymph nodes indicate distant disease, and should be considered a contraindication for surgical resection.

Tumor grade may be as powerful a prognostic factor as tumor size and lymph node status.

Invasion of major retroperitoneal blood vessels predicts poor outcome. The extent of vessel wall involvement is correlated with survival. Patients undergoing portal vein resection for pancreatic cancer have a similar long-term prognosis to patients undergoing standard resection.

PNI is present in most pancreatic tumors. The severity of PNI is a novel prognostic factor.

Tumor cells in the resection margin increase the risk of early deaths. A margin clearance over 1 mm should be achieved. However, additional resection to achieve a negative neck margin after positive frozen section is not recommended due to lack of survival advantage.

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