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

Daniel Åkerberg, Daniel Ansari, Roland Andersson

Department of Surgery, Clinical Sciences Lund, Lund University, and Skåne University Hospital, SE-221 85 Lund, Sweden

Author contributions: Åkerberg D and Ansari D conducted the literature search and drafted the manuscript; Andersson R conceived the study; all authors were involved in manuscript writing and read and approved the final manuscript.

Conflict-of-interest statement: No potential conflicts of interest. No financial support.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript Source: Invited manuscript

Correspondence to: Roland Andersson, MD, PhD, Department of Surgery, Clinical Sciences Lund, Lund University, and Skåne University Hospital, SE-221 85 Lund, Sweden. roland.andersson@med.lu.se Telephone: +46-46-172359

Received: March 24, 2016
Peer-review started: March 25, 2016
First decision: May 12, 2016
Revised: May 24, 2016
Accepted: June 15, 2016
Article in press: June 15, 2016
Published online: July 28, 2016

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

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Åkerberg D, Ansari D, Andersson R. Re-evaluation of classical prognostic factors in resectable ductal adenocarcinoma of the pancreas. World J Gastroenterol 2016; 22(28): 6424-6433 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i28/6424.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i28.6424

INTRODUCTION
Pancreatic cancer has a devastatingly poor prognosis.
The overall survival remains unchanged over a wide period of time with a 5-year survival of 5%-10%[1]. Furthermore, according to recent data, the incidence of pancreatic cancer is increasing[2-4]. 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)[5-9].

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 undefined. 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[10].

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[11]. Larger tumors generally have a greater malignant potential, increasing the risk of tumor involvement of peripancreatic structures[12,13].

However, although most studies indicate impaired survival for larger tumors, a small tumor diameter does not exclude poor prognosis[14,15]. 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[16,17]. 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[18,19].

This, somewhat, unclear relationship between tumor size and prognosis may reflect different tumor biology and invasiveness, independent of tumor size[20], 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 (≥ 60 mo)[21]. 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[22]. 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[23].

Lymph node status may also be defined based
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\textsuperscript{[24]}. The presence of metastases is considered a contraindication to proceed with pancreatic resection.

**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 \textsuperscript{[8]} | 2015 | 968 | ≥ 3 cm              | NR        | Multivariable     | 1.72 (1.16-2.56) | 0.006   |
| Jeong \textsuperscript{[8]}     | 2015 | 276 | < 2.5 cm            | 13 mo     | Multivariable     | 1.65 (1.17-2.32) | 0.004   |
| Hur \textsuperscript{[7]}      | 2015 |     | ≥ 2.5 cm            | 1 mo      | Multivariable     | 1          |         |
|                   |      |     | In situ             | 120 mo    | Multivariable     | 1          |         |
|                    |      |     | < 1.0 cm            | 27 mo     | Multivariable     | 3.09 (2.35-4.07) | < 0.001 |
|                    |      |     | 1.1-2.0 cm          | 17 mo     | Multivariable     | 4.35 (3.42-5.53) | < 0.001 |
|                    |      |     | > 2.0 cm            | 11 mo     | Multivariable     | 5.69 (4.49-7.21) | < 0.001 |
| Yamamoto \textsuperscript{[8]}  | 2015 | 195 | < 2 cm              | 29 mo (mean) | Multivariable | 0.40 (0.17-0.83) | 0.012   |
| Elberms \textsuperscript{[8]}   | 2015 | 1070| < 2 cm              | 19 mo     | Multivariable     | 0.63 (0.50-0.78) | < 0.001 |
| Liu \textsuperscript{[7]}       | 2015 | 411 | > 2 cm              | NR        | Univariable       | 1.46 (1.14-1.88) | 0.003   |
| Okada \textsuperscript{[8]}     | 2014 | 200 | ≥ 3 cm              | NR        | Multivariable     | 3.26 (1.52-7.00) | 0.002   |
| Dusch \textsuperscript{[8]}     | 2014 | 415 | < 3 cm              | 16 mo     | Univariable       | -           | < 0.03  |
| Shin \textsuperscript{[8]}      | 2014 | 537 | ≥ 3 cm              | 22 mo     | Multivariable     | 1.4 (1.13-1.73)  | 0.002   |
| Kooby \textsuperscript{[8]}     | 2014 | 1399| Continuous          | 20 mo     | Multivariable     | 1.12 (1.06-1.18) | < 0.001 |
| Petermann \textsuperscript{[8]} | 2013 | 114 | ≥ 2 cm              | 35 mo     | Multivariable     | 0.52 (0.25-1.05) | 0.071   |
| Jamieson \textsuperscript{[8]}  | 2013 | 217 | ≥ 2 cm              | 35 mo     | Multivariable     | 1.28 (0.93-1.76) | 0.13    |
| Franko \textsuperscript{[8]}    | 2013 | 7135| < 1 cm              | NR        | Multivariable     | 1          |         |
|                   |      |     | 1.1-2 cm            | N0/N1: 28/18 mo | Multivariable | 1.18 (0.94-1.48) | 0.152   |
|                   |      |     | > 2 cm              | N0/N1: 19/14 mo | Multivariable | 1.67 (1.34-2.07) | < 0.001 |
| Lad \textsuperscript{[8]}       | 2013 | 382 | Continuous          | 16 mo     | Multivariable     | 1.23 (1.07-1.41) | 0.003   |
| Sugitaa \textsuperscript{[8]}   | 2013 | 208 | ≥ 3 cm              | NR        | Univariable       | NR         | 0.014   |
| Hong \textsuperscript{[8]}      | 2012 | 209 | < 3 cm              | 20 mo     | Univariable       | NR         | 0.06    |
| Bhatti \textsuperscript{[8]}    | 2010 | 84  | > 2 cm, invasion-    | NR        | Univariable       | NR         | 0.017   |
| Yamada \textsuperscript{[8]}    | 2009 | 335 | ≥ 3 cm              | 11 mo     | Multivariable     | 2.69 (3.05-5.56) | < 0.05  |
| Ueda \textsuperscript{[8]}      | 2009 | 140 | < 3 cm              | 22 mo     | Multivariable     | 1.85 (1.14-3.10) | 0.013   |
| Kaneoka \textsuperscript{[8]}   | 2009 | 84  | ≥ 3 cm              | 11 mo     | Multivariable     | 1          |         |
|                   |      |     | < 2 cm              | NR        | Multivariable     | 1.7 (1.0-3.1)  | 0.031   |
|                   |      |     | > 2-4 cm            | 20 mo     | Multivariable     | 2.3 (1.3-4.5)  | 0.003   |
|                   |      |     | > 4 cm              | 11 mo     | Multivariable     | 1          |         |
| Campbell \textsuperscript{[8]} | 2009 | 163| Continuous          | 14 mo     | Multivariable     | 1.02 (1.00-1.03) | 0.049   |
| Doi \textsuperscript{[8]}       | 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 | Univariable | 1.9 (1.1-3.1)  | 0.018   |
| Zacharias \textsuperscript{[8]} | 2007 | 81 | ≤ 3 cm              | 28 mo     | Multivariable     | 1.24 (1.01-0.51) | 0.04    |
| Pavlik \textsuperscript{[8]}    | 2007 | 905| ≥ 2 cm              | 17 mo     | Multivariable     | 0.46 (0.27-0.78) | 0.004   |
| Moon \textsuperscript{[8]}      | 2006 | 94 | < 3 cm              | 25 mo     | Multivariable     | 1.2 (1.0-1.4)  | 0.01    |
| Cleary \textsuperscript{[8]}    | 2004 | 123| Continuous          | 14 mo     | Univariable       | 1          |         |
| Ahmad \textsuperscript{[8]}     | 2001 | 125| < 2 cm              | 16 mo     | Univariable       | 1.05 (0.58-1.89) | 0.87    |
|                   |      |     | > 2-4 cm            | 16 mo     | Univariable       | 1.15 (0.61-2.15) | 0.66    |
|                   |      |     | > 4 cm              | 21 mo     | Multivariable     | 0.72 (0.37-0.90) | 0.004   |
| Meyer \textsuperscript{[8]}     | 2000 | 462 | ≤ 2 cm              | 28 mo     | Multivariable     | 2.27       | < 0.006 |
|                   |      |     | > 2 cm              | 13 mo     | Multivariable     |           |         |

*OS: Overall survival.*

\textsuperscript{[42]} Akerberg D et al. Prognostic factors in resectable pancreatic cancer
TUMOR GRADE

The WHO classification of tumor grade in pancreatic cancer is based on the original proposal of Klöppel et al.[25] 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[26-28]. Wasi et al.[29] analyzed 8082 patients with resected pancreatic cancer. This study found that high 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[30]. Invasion of major retroperitoneal blood vessels has been found to be an independent predictor of poor survival[11,30,31]. Vascular resections should be performed if it is possible to obtain R0 resections, which is supported by previous histopathological data[32]. 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[33].

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[34]. The lack of perineural involvement may be a good prognostic
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\(27\). 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 cancer, the definition of margin clearance remains a matter of controversy. Further research is needed to establish standardized criteria for margin clearance and to improve patient outcomes.

### 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 et al\(^{[39]}\) | 2015 | 276 | 46 (17) | 16/12 | Multivariable | 1.15 (0.78-1.71) | 0.474 |
| Murakami et al\(^{[42]}\) | 2015 | 937 | 435 (46) | 26/19 | Multivariable | 1.16 (0.89-1.53) | 0.268 |
| Wang et al\(^{[40]}\) | 2014 | 122 | 64 (53) | 31/18 | Multivariable | NR | NS |
| Kelly et al\(^{[42]}\) | 2013 | 492 | 70 (14) | 19/12 | Multivariable | 1.14 (0.83-1.57) | 0.410 |
| Gorg et al\(^{[44]}\) | 2013 | 566 | 119 (21) | 20/13 | Univariable | NR | < 0.050 |
| Castleberry et al\(^{[45]}\) | 2012 | 3592 | 281 (8) | Increased 30-d postoperative mortality, 2.9% vs 5.7% | Multivariable | 2.1 (1.22-3.73) | 0.008 |

### 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 et al\(^{[46]}\) | 2015 | 209 | 197 (94) | 15 | Multivariable | No of PNi< 14:1 14–40: 1.96 (1.01–3.93) >40: 5.81 (3.17–11.35) | < 0.001 |
| Fouquet et al\(^{[47]}\) | 2014 | 166 | 133 (81) | NR | Multivariable | 2.77 (1.40-5.26) | 0.001 |
| Chatterjee et al\(^{[47]}\) | 2012 | 212 | 123 (58) | 29 | Multivariable | 1.70 (1.18-2.45) | 0.005 |
| Takahashi et al\(^{[48]}\) | 2012 | 110 | 56 (51) | NR | Multivariable | 2.48 (1.15-5.52) | 0.026 |
| Sahin et al\(^{[49]}\) | 2012 | 544 | 473 (87) | 29 | Multivariable | 1.60 (1.08-2.36) | 0.019 |
| Robinson et al\(^{[50]}\) | 2012 | 134 | 128 (96) | NR | Multivariable | 5.52 (NR) | < 0.050 |
| Kanda et al\(^{[51]}\) | 2011 | 429 | 148 (34) | NR | Multivariable | 1.72 (1.15-2.58) | < 0.001 |
| Shimada et al\(^{[52]}\) | 2011 | 153 | 146 (94) | 7 (DFS) | Multivariable | 2.19 (1.36-3.52) | 0.001 |
| Murakami et al\(^{[53]}\) | 2010 | 103 | 31 (30) | NR | Multivariable | 1.93 (1.03-3.62) | 0.041 |
| Kazanjan et al\(^{[54]}\) | 2008 | 182 | 112 (62) | 20 | Multivariable | 2.66 (1.74-4.06) | < 0.001 |

OS: Overall survival; PNI: Perineural invasion.
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.

REFERENCES

1. Kos FT, Yazici O, Civelek B, Seker M, Arik Z, Aksoy S, Uncu D, Ozerdem N, Zengin N. Evaluation of the effect of comorbidity on survival in pancreatic cancer by using “Charlson Comorbidity Index” and “Cumulative Illness Rating Scale”. Wein Klin Wochenschr 2014; 126: 36-41 [PMID: 24249323 DOI: 10.1007/s00508-013-0453-9]

2. Akhtar-Danesh GG, Finley C, Akhtar-Danesh N. Long-term trends in the incidence and relative survival of pancreatic cancer in Canada: A population-based study. Pancreatology 2016; 16: 259-265 [PMID: 26804003 DOI: 10.1016/j.pan.2015.12.180]

3. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]

4. Nitecki SS, Sarr MG, Colby TV, van Heerden JA. Long-term survival after resection for ductal adenocarcinoma of the pancreas: Is it really improving? Ann Surg 1995; 221: 59-66 [PMID: 7826162]

5. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini V, Mino-Kenudson M, Fernández-del Castillo C, Lillemoe KD, Grochow LB, Abrams RA. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg 1997; 226: 248-257; discussion 257-260 [PMID: 9339931]

6. Pawlik TM, Gleisner AL, Cameron JL, Winter JM, Assumpcao L, Lillemoe KD, Wolffang C, Hruban RH, Schulick RD, Yeo CJ, Choti MA. Prognostic relevance of lymph node ratio following pancreaticoduodenectomy for pancreatic cancer. Surgery 2007; 141: 610-618 [PMID: 17462460 DOI: 10.1016/j.surg.2006.12.013]

7. Fortner JG, Klimstra DS, Senie RT, Maclean BJ. Tumor size is the primary prognosticator for pancreatic cancer after regional pancreatectomy. Ann Surg 1996; 223: 147-153 [PMID: 8597580]

8. Panici A, Hosokawa P, Henderson W, Schulick RD, Eidi BH, McCarter MD, Gajdos C. Characteristics of 10-Year Survivors of Pancreatic Ductal Adenocarcinoma. JAMA Surg 2015; 150: 701-710 [PMID: 26062046 DOI: 10.1001/jamasurg.2015.068]

9. Ferrone CR, Pieretti-Vanmarcke R, Bloom JP, Zheng H, Szymonikia J, Wargo JA, Thayer SP, Lauwers GY, Deshpande V, Mino-Kenudson M, Fernández-del Castillo C, Lillemoe KD, Warshaw AL. Pancreatic ductal adenocarcinoma: long-term survival does not equal cure. Surgery 2012; 152: S43-S49 [PMID: 22763261 DOI: 10.1016/j.surg.2012.05.020]

10. Petermann D, Demartines N, Schäfer M. Is tumour size an underestimated feature in the current TNM system for malignancies of the pancreatic head? HPB (Oxford) 2013; 15: 87-881 [PMID: 23458601 DOI: 10.1111/hpb.12052]

11. Jamieson NB, Foulis AK, Oien KA, Dickson EJ, Imrie CW, Carter R, McKay CJ. Peripancreatic fat invasion is an independent predictor of poor outcome following pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. J Gastrointest Surg 2011; 15: 512-524 [PMID: 21116727 DOI: 10.1007/s11605-013-1954-4]

12. Warren BF. Resection margins and R1 rates in pancreatic cancer—where are we then? Histopathology 2008; 53: 599; author reply 599
Weitz J, Büchler MW. Surgery insight: surgical management of pancreatic cancer. Nat Clin Pract Oncol 2007; 4: 26-53. DOI: 10.1038/ncponc0925

Franko J, Huey P, Lopes TL, Goldman CD. Survival among pancreaticoduodenectomy patients treated for pancreatic head cancer & I; or 1 cm. Ann Surg Oncol 2013; 20: 357-361. PMID: 22941171 DOI: 10.1245/s10434-012-2621-y

Shin SH, Kim SC, Hong SM, Song KB, Lee JH, Park KM, Lee YJ. Can statistically determined prognostic factors predict the long-term survival of patients with pancreatic ductal adenocarcinoma following surgical resection?: Clinico-pathological analysis of 82 long-term survivors. Pancreas 2014; 43: 571-577. PMID: 24681875 DOI: 10.1097/MPA.0000000000000633

Izumi S, Nakamura S, Mano S, Onoda Y. Well-differentiated pancreatic ductal adenocarcinoma measuring ≤ 1 cm exhibit early features of tumor progression: a report of five lesions and a comparative study with advanced lesions. Surg Today 2014; 44: 2058-2064. DOI: 10.1007/s11295-013-0804-1

Hurt C, Tramontano AC, Dowling EC, Brooks GA, Jeon A, Brugge WR, Gazelle GS, Kong CY, Pandharipande PV. Early Pancreatic Ductal Adenocarcinoma Survival Is Dependent on Size: Positive Implications for Future Targeted Screening. Pancreas 2015; Epub ahead of print. DOI: 10.1097/MPA.0000000000000587

Hong SM, Goggins M, Wolfgang CL, Schulick RD, Edil BH, Cameron JL, Handra-Luca A, Herman JM, Hruban RH, Jagannath S, Jimenez RE, Karp AS, Langer S, Langer P, Langer G, Gallinger S. Prognostic factors in resected pancreatic adenocarcinoma: analysis of actual 5-year survivors. J Am Coll Surg 2004; 198: 722-731. PMID: 15110805 DOI: 10.1016/j.jamcollsurg.2004.01.008

Dusch N, Weiss C, Ströbel P, Kienle P, Post S, Niedergethmann M. Factors predicting long-term survival following pancreatic resection for ductal adenocarcinoma of the pancreas: a population-based analysis. Ann Surg Oncol 2008; 15: 165-174. PMID: 17896141 DOI: 10.1245/s10434-007-9587-1

Tol JA, Gouma DJ, Bussch A, Verhees CJ, Montorsio M, Adham M, Andren-Sandberg A, Aslan SJ, Bockhorn M, Büchler MW, Conlon KC, Fernández-Cruz L, Fij dredt P, Fries H, Hartwig W, Izbicki JR, Lilleemo K, Milcicvevic MN, Neoptolemos JP, Shrikhande SV, Volmer CM, Yeo CJ, Charney RM. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surgery 2014; 156: 591-600. DOI: 10.1016/j.surg.2014.06.016

Schwarz L, Lupinacci RM, Sivick M, Leszczak M, Buehnen M, Vuarinesson H, Balladur P, Paye F. Para-aortic lymph node sampling in pancreatic head adenocarcinoma. Br J Surg 2014; 101: 530-538. DOI: 10.1111/bjs.13444

Klöppel G, Lingenthal G, von Bülow M, Kern HF. Histological and fine structural features of pancreatic ductal adenocarcinomas in relation to growth and prognosis: studies in xenografted tumours and clinico-histopathological correlation in a series of 75 cases. Histopathology 1985; 9: 841-856. PMID: 2997015

Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. Ann Surg 2003; 237: 174-85. PMID: 12496533 DOI: 10.1097/01.SLA.0000041 266.10047.38

Kuhlmann KF, de Castro SM, Wesseling JG, ten Kate FJ, Offerhaus GJ, Busch OR, van Gulik TM, Obertop H, Gouma DJ. Surgical treatment of pancreatic adenocarcinoma: actual survival and prognostic factors in 343 patients. Eur J Cancer 2004; 40: 549-558. DOI: 10.1016/j.ejca.2003.10.026

Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, Hodgkin MB, Sauter PK, Hruban RH, Riall TS, Schulick RD, Choti MA, Lilleemo KD, Yeo CJ. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. J Gastrointest Surg 2006; 10: 1199-1210. discussion 1210-1211 PMID: 17114007 DOI: 10.1016/j.gassur.2006.08.018

Wasif N, Ko CY, Farrell J, Wainberg Z, Hines OJ, Reber H, Tomlinson JS. Impact of tumor grade on prognosis in pancreatic cancer: should we include grade in AJCC staging? Ann Surg Oncol 2010; 17: 2312-2320. PMID: 1245/s10434-010-1071-7

Fukuda S, Oussoultzoglou E, Bachellier P, Rosso E, Nakano H, Autet M, Jaeck D. Significance of the depth of portal vein wall invasion after curative resection for pancreatic adenocarcinoma. Arch Surg 2017; 142: 172-179. PMID: 17390969 DOI: 10.1001/archsurg.142.2.172

Liu L, Katz MH, Lee SM, Fischer LK, Prakash L, Parker N, Wang H, Varadachary GR, Wolff RA, Lee JE, Pisters PW, Maitra A, Fleming JB, Estrella J, Rashid A, Wang H, Superior Mesenteric Artery Margin of Posttherapy Pancreaticoduodenectomy and Prognosis in Patients With Pancreatic Ductal Adenocarcinoma. Ann Surg 2015; 39: 1395-1403. PMID: 26200098 DOI: 10.1097/01.sla.0000000000000491

Rehders A, Steecklin NH, Güray A, Riediger R, Alexander A, Knoefel WT. Vascular invasion in pancreatic cancer: tumor biology or tumor topography? Surgery 2012; 152: S143-S151. PMID: 22766363 DOI: 10.1058/0005-13-2408-v

Mollberg N, Rahbari NN, Koch M, Hartwig H, Hoeger Y, Bückel MW, Weitz J. Arterial resection during pancreatoduodenectomy for pancreatic cancer: a systematic review and meta-analysis. Ann Surg 2011; 254: 882-893. DOI: 10.1097/SLA.0b013e31823ac299

Bourguet T, Germain A, Brunaud L, Bresler A, Ayav A. Is perineural invasion more accurate than other factors to predict early recurrence after pancreatoduodenectomy for pancreatic head adenocarcinoma? World J Surg 2014; 38: 2132-2137. PMID: 24715041 DOI: 10.1007/s00268-014-2465-7

Shimada K, Nara S, Esaki M, Sakamoto Y, Kusuge T, Hiroya N. Intrapancreatic nerve invasion as a predictor for recurrence after pancreatoduodenectomy in patients with invasive ductal carcinoma of the pancreas. Pancreas 2011; 40: 464-468. PMID: 21289526 DOI: 10.1097/MPA.0b013e31820d5a97

Kondo N, Murakami Y, Uemura K, Hashimoto Y, Nakagawa S, Sasaki H, Sueda T. An Increased Number of Perineural Invasions Is Independently Associated With Poor Survival of Patients With Resectable Pancreatic Ductal Adenocarcinoma. Pancreas 2015; 44: 1345-1351. PMID: 26465957 DOI: 10.1097/ 01.mpa.0000000000000413

Kooby DA, Lad NL, Squires MH, Maithel SK, Sarmiento JM, Staley CA, Adsvey NV, El-Rayes BF, Lysiew SM, Estrella J, Rashid A, Wang H, Varadachary GR, Wolff RA, Lee JE, Pisters PW, Maitra A, Fleming JB, Estrella J, Rashid A, Wang H, Superior Mesenteric Artery Margin of Posttherapy Pancreaticoduodenectomy and Prognosis in Patients With Pancreatic Ductal Adenocarcinoma. Ann Surg 2011; 254: 882-893. PMID: 22064622 DOI: 10.1097/ SLA.0b013e31823ac299

Matsumoto I, Murakami Y, Shiniwe M, Asahi S, Goto T, Tani M, Motoi F, Uemura K, Shio M, Sato S, Honda G, Yamaue H, Unno
M, Akahori T, Kwon AH, Kurata M, Ajiki T, Fukumoto T, Ku Y. Proposed preoperative risk factors for early recurrence in patients with resectable pancreatic ductal adenocarcinoma after surgical resection: A multi-center retrospective study. *Pancreatology* 2015; 15: 674-680 [PMID: 26467797 DOI: 10.1016/j.pan.2015.08.008]

39 Jeong J, Choi DW, Choi SH, Heo JS, Jang KT. Long-term outcome of portomesenteric vein invasion and prognostic factors in pancreatic head adenocarcinoma. *ANZ J Surg* 2015; 85: 264-269 [PMID: 24641800 DOI: 10.1111/ans.12502]

40 Yamamoto T, Yagi S, Kinoshita H, Sakamoto Y, Okada K, Uryuha K, Moritomo T, Kaihara S, Hosotani R. Long-term survival after resection of pancreatic cancer: a single-center retrospective analysis. *World J Gastroenterol* 2015; 21: 262-268 [PMID: 25574100 DOI: 10.3748/wjg.v21.i1.262]

41 Elberm H, Ravikumar R, Sabin C, Abu Hilal M, Al-Hilli A, Arooi S, Bond-Smith G, Bramhall S, Coldham C, Hammond J, Hutchins R, Imber C, Preziosi G, Saleh A, Silva M, Simpson J, Spoletin G, Stell D, Terrace J, White S, Wigmore S, Fusai G. Outcome after pancreaticoduodenectomy for T3 adenocarcinoma: A multivariable analysis from the UK Vascular Resection for Pancreatic Cancer Study Group. *Eur J Surg Oncol* 2015; 41: 1500-1507 [PMID: 26346183 DOI: 10.1016/j.ejso.2015.08.158]

42 Okada S, Okusaka T, Ishii H, Kyogoku A, Yoshimori M, Kajimura N, Yamaguchi K, Kakizoe T. Elevated serum interleukin-6 levels in patients with pancreatic cancer. *Jpn J Clin Oncol* 1998; 28: 12-15 [PMID: 9491135]

43 Jamieson NB, Chan NI, Foulis AK, Dickson EJ, McKay CJ, Carter CR. The prognostic influence of resection margin clearance following pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. *J Gastrointest Surg* 2013; 17: 511-521 [PMID: 23297028 DOI: 10.1007/s11605-012-2131-z]

44 Lad NL, Squires MH, Mathiokel SK, Fisher SB, Mehta VV, Cardona K, Russell MC, Staley CA, Adsay NV, Kooby DA. Is it time to stop checking frozen section neck margins during pancreaticoduodenectomy? *Am J Surg Oncol* 2015; 20: 3626-3633 [PMID: 23838098 DOI: 10.1245/s10434-013-3080-9]

45 Sugitara T, Uesaka K, Mihara K, Sasaki K, Kanemoto H, Mizuno T, Okamura Y. Margin status, recurrence pattern, and prognosis after resection of pancreatic cancer. *Surgery* 2013; 154: 1078-1086 [PMID: 23973112 DOI: 10.1016/j.surg.2013.04.015]

46 Bhatti I, Peacock O, Awan AK, Semeraro D, Larvin M, Hall RI. Lymph node ratio versus number of affected lymph nodes as predictors of survival for resected pancreatic adenocarcinoma. *World J Surg* 2010; 34: 768-775 [PMID: 20052471 DOI: 10.1007/s00268-009-0336-4]

47 Yamada S, Nakao A, Fujii T, Sugimoto H, Kanazumi N, Nomoto S, Koderia Y, Takeda S. Pancreatic cancer with paraaortic lymph node metastasis: a contraindication for radical surgery? *Pancroas* 2009; 38: e13-e17 [PMID: 18797422 DOI: 10.1097/MPA.0b013e3181889e2d]

48 Ueda M, Endo I, Nakashima M, Minami Y, Takeda K, Matsuo K, Nagano Y, Tanaka K, Ichikawa Y, Togo S, Kanisaki C, Shimada H. Prognostic factors after resection of pancreatic cancer. *World J Surg* 2009; 33: 104-110 [PMID: 19011933 DOI: 10.1007/s00268-009-9807-2]

49 Kaneoka Y, Yamaguchi A, Isogai M. Portal or superior mesenteric vein resection for pancreatic head adenocarcinoma: prognostic value of the length of venous resection. *Surgery* 2009; 145: 417-425 [PMID: 19303991 DOI: 10.1016/j.surg.2008.12.009]

50 Campbell F, Smith RA, Whelan P, Sutton R, Ratlry M, Neoptolemos JP, Ghanem P. Classification of R1 resections for pancreatic cancer: the prognostic relevance of tumour involvement within 1 mm of a resection margin. *Histopathology* 2009; 55: 277-283 [PMID: 19723142 DOI: 10.1111.j.1365-2559.2009.03376.x]

51 Doi R, Kani K, Ito D, Fujimoto K, Kawaguchi Y, Wada M, Kogire M, Hosotani R, Imamura M, Uemoto S. Prognostic implication of para-aortic lymph node metastasis in resectable pancreatic cancer. *World J Surg* 2007; 31: 147-154 [PMID: 17171496 DOI: 10.1007/s00268-005-0730-5]

52 Zacharias T, Jaekc D, Oussoultzoglou E, Neuville A, Bacheller P. Impact of lymph node involvement on long-term survival after R0 pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas. *J Gastrointest Surg* 2007; 11: 350-356 [PMID: 17458610 DOI: 10.1007/s11605-007-0197-3]

53 Moon HJ, An JY, Heo JS, Choi SH, Joh JW, Kim YI. Predicting survival after surgical resection for pancreatic ductal adenocarcinoma. *Pancreas* 2006; 32: 37-43 [PMID: 16340742]
Portal vein mesentericopancreatic resection safe and worthwhile?  
Boudjema K, Wolf PD, Jaeck D. Is pancreaticoduodenectomy with mesentericopancreatic vein involvement.

Pancreatoduodenectomy with vascular resection: margin status and survival duration.

Pancreaticoduodenectomy combined with vascular resection and reconstruction for patients with locally advanced pancreatic cancer: a multicenter, retrospective analysis.

The impact of vascular resection on early postoperative outcomes after pancreaticoduodenectomy: an analysis of the American College of Surgeons National Surgical Quality Improvement Program database.

Chakravarty KD, Hsu JT, Liu KH, Yeh CN, Yeh TS, Hwang TL, Jan YY, Chen MF. Prognosis and feasibility of en bloc resection in stage II pancreatic adenocarcinoma.

Ouaisi M, Hubert C, Verhelst R, Astarci P, Sempoux C, Jouret-Mourin A, Loundou A, Gigot JF, Multidisciplinary HPB Group of Center of Cancer. Vascular reconstruction during pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head.

Kurosaki I, Hatakeyama K, Minagawa M, Sato D. Portal vein resection in surgery for cancer of biliary tract and pancreas: special reference to the relationship between the surgical outcome and site of primary tumor. J Gastrointest Surg 2008; 12: 907-918 [PMID: 19666202 DOI: 10.1007/s11605-007-0387-5]

Carrière N, Sautter A, Gaudry D, Kianmehr R, Vullierme MP, Couvelard A, Ruszniewski P, Belghiti J. Pancreaticoduodenectomy with mesentericopancreatic vein resection for adenocarcinoma of the pancreatic head. World J Gastroenterol 2010; 34: 2648-2661 [PMID: 20607257 DOI: 10.3748/wjg.v16.i10.696-6]

Shimada K, Sano T, Sakamoto Y, Kusako T. Clinical implications of combined portal vein resection as a palliative procedure in patients undergoing pancreaticoduodenectomy for adenocarcinoma of pancreas. Ann Surg Oncol 2006; 13: 1569-1578 [PMID: 17009145 DOI: 10.1245/s10434-006-9143-4]

Tseng JF, Raut CP, Lee JE, Pisters PW, Vauthey JN, Abdalla EK, Gomez HF, Sun CC, Crane CH, Wolff RA, Evans DB. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. J Gastrointest Surg 2004; 8: 935-949; discussion 949-950 [PMID: 15585381 DOI: 10.1016/j.gassur.2004.09.046]

Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, Yeung C, Wong J. Pancreaticoduodenectomy with en bloc portal vein resection for pancreatic carcinoma with suspected portal vein involvement. World J Surg 2004; 28: 602-608 [PMID: 15366755]

Nakagohri T, Kinoshita T, Konishi M, Inoue K, Takahashi S. Survival benefits of portal vein resection for pancreatic cancer. Am J Surg 2003; 186: 149-153 [PMID: 12885608]

Bacheller P, Nakano H, Oussoultzoglou PD, Weber JC, Boudjema K, Wolf PD, Jaeck D. Is pancreaticoduodenectomy with mesentericopancreatic venous resection safe and worthwhile? Am J Surg 2001; 182: 120-129 [PMID: 11574081]

Chatterjee D, Katz MH, Rashid A, Wang H, Inga AC, Varadhachary GR, Wolff RA, Lee JE, Pisters PW, Crane CH, Gomez HF, Abbruzzese JL, Fleming JB, Wang H. Perineural and intranodal and vascular invasion in posttherapeutic pancreaticoduodenectomy specimens predicts poor prognosis in patients with pancreatic ductal adenocarcinoma. Am J Surg Pathol 2012; 36: 409-417 [PMID: 22301497 DOI: 10.1097/PAS.0b013e31824104e5]

Takahashi H, Ohigashi H, Ishikawa O, Gotoh K, Yamada T, Nagata S, Tomita Y, Eguchi H, Doki Y, Yano M. Perineural invasion and lymph node involvement as indicators of surgical outcome and pattern of recurrence in the setting of preoperative gemcitabine-based chemoradiation therapy for resectable pancreatic cancer. Am J Surg 2012; 255: 95-102 [PMID: 22123160 DOI: 10.1016/J.SLA.2011.03.28131c]

Sahin IH, Shama MA, Tanaka M, Abbruzzese JL, Curley SA, Hassam M, Li D. Association of diabetes and perineural invasion in pancreatic cancer. Cancer Med 2012; 1: 357-362 [PMID: 23422285 DOI: 10.1002/cam4.43]

Kazanjian KK, Hines OJ, Duffy JP, Yoon DY, Cortina G, Reber HA. Improved survival following pancreaticoduodenectomy to treat adenocarcinoma of the pancreas: the impact of operative blood loss. Arch Surg 2008; 143: 1166-1171 [PMID: 19075167 DOI: 10.1001/archsurg.143.12.1166]

Konstantinidis IT, Warshaw AL, Allen JN, Blazowski LS, Castillo CF, Deshpande V, Hong TS, Kwak EL, Lauwers GY, Ryan DP, Wargo JA, Lillemoe KD, Ferrone CR. Pancreatic ductal adenocarcinoma: is there a survival difference for R1 resections versus locally advanced unresectable tumors? What is a “true” R0 resection? Ann Surg 2013; 257: 731-736 [PMID: 22968073 DOI: 10.1097/SLA.0b013e318286d2a2]

Kimbrough CW, St Hill CR, Martin RC, McMasters KM, Scoggins CR. Tumor-positive resection margins reflect an aggressive tumor biology in pancreatic cancer. J Surg Oncol 2013; 107: 602-607 [PMID: 23450687 DOI: 10.1002/jso.23299]

Gnerlich JL, Luka SR, Deshpande AD, Dubray BJ, Weir JS, Carpenter DH, Brunet EM, Straub SM, Hawkins WG, Linehan DC. Microscopic margins and patterns of treatment failure in resected pancreatic adenocarcinoma. Arch Surg 2012; 147: 753-760 [PMID: 22911074 DOI: 10.1001/archsurg.2012.1126]

Van den Broeck A, Sergeant G, Ectors N, Van Steenbergen W, Janssens P, Ceelen W, Mathisen O, Clausen OP, Gladhaug IP. Resectable adenocarcinoma of the pancreas: the retroperitoneal resection. J Gastrointest Surg 2004; 8: 600-604 [PMID: 15131205 DOI: 10.1016/j.jgs.2003.12.006]

Chang DK, Johns AL, Merrett ND, Gill AJ, Colvin EK, Scarlett CJ, Nguyen NQ, Leong RW, Cosman PC, Kelly MJ, Sutherland RL, Henshall SM, Kench JG, Biankin AV. Margin clearance and outcome in resected pancreatic adenocarcinoma. J Clin Oncol 2009; 27: 2855-2862 [PMID: 19398572 DOI: 10.1200/JCO.2008.20.5104]

Westgaard A, Tafjord S, Farstad IN, Cvancarova M, Eide TJ, Mathisen O, Clausen OP, gladhaug IP. Pancreaticoduodenectomy combined with vascular resection and reconstruction for patients with locally advanced pancreatic cancer. Ann Surg Oncol 2010; 2855-2862 [PMID: 19398572 DOI: 10.1200/JCO.2008.20.5104]

Westgaard A, Tafjord S, Farstad IN, Cvancarova M, Eide TJ, Mathisen O, Clausen OP, Gladhaug IP. Resectable adenocarcinomas in the pancreatic head: the retroperitoneal resection. J Gastrointest Surg 2004; 8: 600-604 [PMID: 15366755]

Shahin IH, Shama MA, Tanaka M, Abbruzzese JL, Curley SA, Hassam M, Li D. Association of diabetes and perineural invasion in pancreatic cancer. Cancer Med 2012; 1: 357-362 [PMID: 23422285 DOI: 10.1002/cam4.43]

Kazanjian KK, Hines OJ, Duffy JP, Yoon DY, Cortina G, Reber HA. Improved survival following pancreaticoduodenectomy to treat adenocarcinoma of the pancreas: the impact of operative blood loss. Arch Surg 2008; 143: 1166-1171 [PMID: 19075167 DOI: 10.1001/archsurg.143.12.1166]
Resection accomplished with minimal postoperative complications is the surgeon’s contribution to long-term survival in pancreatic cancer. J Gastrointest Surg 2006; 10: 1338-1345; discussion 1345-1346 [PMID: 17175452 DOI: 10.1016/j.gassur.2006.09.008]

P- Reviewer: Kleeff J, Yang F, Zhang ZM
S- Editor: Ma YJ
L- Editor: A
E- Editor: Ma S

Åkerberg D et al. Prognostic factors in resectable pancreatic cancer
