

Recent Advances in Pancreatic Cancer Surgery of Relevance to the Practicing Pathologist

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KEYWORDS

- Whipple • Pancreatoduodenectomy • Pancreas • Surgery • Pathology • Lymph node
- Neoadjuvant • Radiofrequency ablation

Key points

- Pancreatic cancer remains one of the most deadly cancers, and only 20% of patients are eligible for surgery.
- Both the total number and the ratio of lymph node metastases are strong prognostic factors in pancreatic cancer, but extended lymphadenectomy does not improve survival.
- Initially borderline resectable and nonresectable disease may be downstaged to resectable disease in approximately 30% to 40% of patients following neoadjuvant chemotherapy.
- Local ablative therapies for locally advanced disease, such as radiofrequency ablation and irreversible electroporation, may offer a survival benefit compared with current standard palliative chemotherapy but trials will have to be awaited.

ABSTRACT

Recent advances in pancreatic surgery have the potential to improve outcomes for patients with pancreatic cancer. We address 3 new, trending topics in pancreatic surgery that are of relevance to the pathologist. First, increasing awareness of the prognostic impact of intraoperatively detected extraregional and regional lymph node metastases and the international consensus definition on lymph node sampling and reporting. Second, neoadjuvant

chemotherapy, which is capable of changing 10% to 20% of initially unresectable, to resectable disease. Third, in patients who remain unresectable following neoadjuvant chemotherapy, local ablative therapies may change indications for treatment and improve outcomes.

OVERVIEW

Pancreatic cancer remains one of the deadliest forms of cancer, with an overall 5-year survival

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rate of 3% to 6%.^{1–3} By 2030, pancreatic cancer is projected to become the number 2 cause of cancer-related deaths in Western countries.⁴ Although patients with resectable disease relatively have the best prognosis, they represent only 20% of the population with pancreatic cancer, and overall survival following surgery in these patients is still only 20 months.^{5–8} Patients with nonresectable disease may be divided into patients with locally advanced or metastatic disease, each representing approximately 40% of the total population. Locally advanced pancreatic cancer (LAPC) precludes a resection due to extensive involvement of important vascular structures, such as the celiac trunk, superior mesenteric artery, superior mesenteric vein, and portal vein.⁹ Survival of patients with LAPC is approximately 10 months following standard chemotherapy treatment with gemcitabine.^{10–12} In patients with metastatic disease, survival is approximately 7 months following palliative treatment with gemcitabine.¹³

There have been several recent advances in treatment for patients with pancreatic cancer. For example, FOLFIRINOX (a combination of 5-fluorouracil [5-FU], oxaliplatin, irinotecan, and leucovorin) is a relatively new chemotherapy regimen and has demonstrated a significant survival benefit up to approximately 11 months in the metastatic setting, although it is generally reserved for fitter patients (World Health Organization performance status 0–1) due to the increased toxicity profile.¹³ In surgical patients, postoperative mortality has dropped to approximately 1% to 2% in very high volume centers, although the complication rate remains high at approximately 50%.⁶ As research is progressing rapidly, we describe 3 new and trending topics in pancreatic surgery, which are of relevance to the practicing pathologist. These include the intraoperative assessment of lymph nodes, neoadjuvant treatment to induce tumor resectability in patients with initially nonresectable or borderline resectable disease, and 2 emerging local ablative therapies for LAPC: irreversible electroporation (IRE) and radiofrequency ablation (RFA).

EXAMINATION OF LYMPH NODES

Nodal metastases are a strong prognostic factor for survival after surgery in patients with pancreatic cancer.¹⁴ Recent studies have however demonstrated that the lymph node ratio, the number of lymph nodes with metastases divided by the total number of excised lymph nodes, and the total amount of resected positive nodes have significant prognostic value.^{15,16} This stresses the importance of identifying all lymph nodes in

surgical specimens with pancreatic cancer. There is, however, no therapeutic impact of extensive lymphadenectomy. Five randomized controlled trials found no survival benefit when comparing extended to standard lymphadenectomy during pancreatoduodenectomy for pancreatic cancer.^{17–21}

Until recently, the interpretation of these data was difficult due to different definitions of “standard” and “extended” lymphadenectomy in pancreatoduodenectomy. Hence, in 2014, the International Study Group of Pancreatic Surgery (ISGPS) published a definition of a standard lymphadenectomy based on the available literature and consensus statements formulated during several expert meetings.²² The consensus statement included the following lymph nodes (classified according to the Japanese Pancreas Society, **Fig. 1**) as part of a standard lymphadenectomy: 5, 6, 8a, 12b1-2, 12c, 13a-b, 14a-b and 17a-b.²³

The ISGPS definition was designed for pancreatic ductal adenocarcinoma, but is advised for all pancreatoduodenectomies. According to the current seventh edition of the TNM classification, however, not all lymph nodes included in the ISGPS standard lymphadenectomy are always considered as regional nodes.²⁴ For example, lymph node 8a (hepatic artery) is regarded as a regional node in case of pancreatic carcinoma, but as an extraregional node in case of an ampullary tumor. This would imply that the impact of frozen section analysis of this lymph node during pancreatoduodenectomy could depend on the type of cancer, which, however, may be difficult to determine at that stage.

Furthermore, the ISGPS did not include para-aortic lymph nodes in the standard resection, as para-aortic lymph node metastases are strongly related to decreased survival.^{25–28} Available evidence on survival following pancreatic resection in the presence of various intraoperatively detected lymph node metastases consists of small, retrospective studies with selection bias. It has become clear that especially para-aortic lymph node metastases predict poor survival after pancreatoduodenectomy. Large prospective studies are needed to create clinical risk models to determine whether exploration should be aborted once these lymph node metastases are detected.

Standardized pathologic examination of lymph nodes, and of lymph node classification is crucial to allow valid comparison of study results. To optimize this process, lymph nodes could be sent for pathologic analysis separately, by the surgeon. A clear description of the total amount of identified nodes, both positive and negative, and which

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