

Clinical Significance of Intraoperative Frozen Section Analysis of Pancreatic Cancer Surgical Margin at the Time of Pancreaticoduodenectomy

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Rezumat

Importanța clinică a examenului histopatologic intraoperator extemporanu al marginilor chirurgicale în timpul duodenopancreatectomiei în cancerul pancreatic

Date generale: În zilele noastre, obținerea unei rezecții R0 este unul dintre cei mai importanți factori independenți de prognostic al supraviețuirii pe termen lung în managementul cancerelor pancreatice. Scopul acestui studiu este de a evalua importanța clinică a examenului histopatologic intraoperator extemporanu al marginilor chirurgicale pancreatice în timpul duodenopancreatectomiei pentru cancer pancreatic.

Materiale și metode: Am efectuat o analiză retrospectivă a datelor culese prospectiv de la 37 de pacienți operați pentru cancer de cap de pancreas și evaluați în privința marginilor chirurgicale prin examen histopatologic intraoperator extemporanu, în perioada septembrie 2013-august 2014 în cadrul centrului nostru.

Rezultate: Vârsta medie a pacienților a fost de 64,55 ani (între 19 și 82 ani), dimensiunea medie a tumorii a fost de 3,96 cm (între 1,16-6,25 cm), iar numărul mediu de ganglioni recoltați a fost de 18,52 (între 9 și 45). La examenul histopatologic intraoperator extemporanu un pacient a prezentat margini pozitive (2,7%), fiind supus pancreatectomiei totale sau complementare.

Concluzii: Asigurarea unei rezecții cu margini chirurgicale negative intraoperator prin examen histologic extemporanu

poate crește rata rezecțiilor R0 în cancerul de pancreas. Estimarea preoperatorie a marginilor tumorale prin ecoendoscopie, tomografie computerizată sau rezonanță magnetică în general se corelează cu descoperirile intraoperatorii, însă în cazurile suspecte este recomandat examenul histopatologic intraoperator extemporanu.

Cuvinte cheie: cancer pancreatic, examen histopatologic, recidivă

Abstract

Background: Today, in the management of pancreas cancers, achieving an R0 resection is one of the most powerful independent predictors of long-term survival. The aim of this study is to assess the clinical significance of intraoperative frozen section analysis of the pancreatic surgical margin for pancreatic cancer during pancreaticoduodenectomy.

Material and Methods: We conducted a retrospective analysis of prospectively collected data of 37 patients who were operated for pancreatic head cancer and who were evaluated for surgical margin by frozen section analysis intraoperatively, between September 2013 and August 2014 in our center. The intraoperative biopsy reports were compared with final pathological reports.

Results: The mean age of the patients was 64.55(19-82) years (range), the mean tumor size was 3.96(1.16-6.25) cm (range) and the mean harvested lymph node number was 18.52(9-45) (range). In the intraoperative frozen section, one patient was positive for surgical margin (2.7%) who underwent total or complementary pancreatectomy.

Conclusion: To secure a tumor-free margin by frozen section, intraoperatively, may increase R0 resection rate in pancreas

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cancers. The preoperative estimation of tumor margin by endoscopic ultrasonography, computerized tomography or magnetic resonance imaging mostly correlate with intraoperative findings, however in suspected cases intraoperative frozen section for margin determination should be performed.

Key words: pancreatic cancer, pathological examination, cancer recurrences

Introduction

Tumors of the pancreas treated by pancreaticoduodenectomy carries one of the most dismal prognoses among the gastrointestinal cancers despite advances in diagnostic imaging and endoscopic modalities, resection techniques and perioperative care (1).

The median overall survival of patients who undergo complete resection with negative margins ranges between 12 and 26 months. Although there are many therapeutic modalities for treatment of such tumors, complete surgical R0 resection is the superior treatment modality for patients with resectable disease until more effective systemic therapy is discovered (2,3). This is predicated on the notion that, by extending the degree of pancreatic resection, one will eventually achieve an R0 resection; the basis of the old adage that your operation is only as good as your worst margin.

Complete tumor extirpation with negative margin status is regarded as an important principle of surgical oncology influencing overall survival (4,5). For that reason, intraoperative frozen section analysis of margins of resection has been obtained traditionally by many pancreatic surgeons. A positive intraoperative frozen section usually gives rise to extending resections of tumor-bearing tissues, especially at the pancreatic and biliary margins. However, the impact of negative margin status on overall survival remains to be clarified (6,7).

In the literature, there is no evidence of routine application of intraoperative frozen section analysis for surgical margins during pancreaticoduodenectomy except in doubtful cases in which it may increase the possibility of R0 resection. With the advent of perioperative diagnostic imaging and endoscopic modalities, it is also possible to plan the surgical treatment in an effective way which may cause to decrease the need for intraoperative frozen section analysis (8-10).

The aim of this study is to investigate the effectiveness and necessity of frozen section analysis of surgical margins during pancreaticoduodenectomy.

Material and Methods

Patients

Between September 2013 and August 2014, 37 pancreatic tumor patients treated by pancreaticoduodenectomy were enrolled in the study (Table 1). Patients with ampullary

Table 1. The demographic data of our patients

Age(mean)	64.55 (19-82)
Gender F/M	20/17
Mean lenfadenopathy	18,52 (9-45)
Mean tumor diametre	3,96 (1,16-6,25)
Tumor localization	
Pancreatic head	33 (%89,1)
Periampullary	4 (%10,9)

tumors, and patients who received neoadjuvant therapies were excluded from the study. All patients with lack of evidence for unresectability underwent surgical exploration. Metastatic diseases, involvement of superior mesenteric and celiac arteries were accepted as criteria of unresectability. Pylorus preserving pancreaticoduodenectomy was performed by a single surgeon in standard fashion. The extent of the pancreatic resection was defined before the surgery according to the diagnostic imaging and endoscopic data, and modified during the surgery according to frozen section analysis of the surgical margins. PD was performed in a standard fashion, as previously described. The most oncologically important part of the operation was the final step involving division of the pancreas and completion of the mesenteric and retroperitoneal dissection by removing all soft tissue to the right of the adventitia of the SMA, ie, the SMA margin. Tangential or segmental resection of the SMV, PV, or SMPV confluence was performed when the operating surgeon could not separate the pancreatic head and/or the uncinate process from the SMPV confluence without leaving gross tumor on the vein or risking a venotomy. After taking the specimen out of the patient, all margins were marked with sutures. Sutures were placed to the neck of the pancreas (pancreatic surgical margin), to the uncinate process with retroperitoneal part of the pancreas (retroperitoneal – uncinate surgical margin), and to common bile duct/common hepatic duct (biliary surgical margin). The specimen was sent to frozen analysis room and waited until the response declared. If the margins were negative, the reconstruction process was performed.

But positive intraoperative margins necessitate extended resections to obtain a negative margin. A permanent section analysis was also performed to all frozen section evaluations.

The data of the patients including age, gender, and pathological analysis of both frozen and permanent sections were recorded.

Pathologic assessment

All resection specimens were dissected and reported by the same pathologist. On receipt of the specimen from the operating room the surgical margins of the pancreatic neck, bile duct, duodenum and the retroperitoneal pancreatic area are examined macroscopically and the tissue is submitted for frozen section analysis (Fig. 1). Complete en face sections through the pancreatic and common bile duct margins were

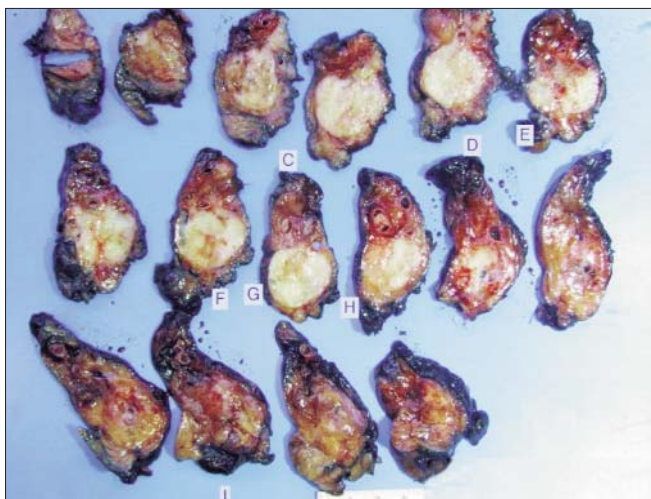


Figure 1. The specimen from the operating room the surgical margins of the pancreatic neck (C,D,E,F), bile duct (G), duodenum (H) and the retroperitoneal pancreatic area (I) are examined macroscopically and the tissue is submitted for frozen section analysis

sampled. The duodenum and bile duct are opened along its way. The retroperitoneal margin of the pancreatic dissection area including the vascular groove is inked. Five resection margins were examined at paraffine blocks: Proximal gastric / duodenal margins, distal duodenal margin, pancreatic distal margin (Fig. 2 A), common bile duct margin and retroperitoneal uncinata margin (Fig. 2 B). The opened duodenum and bile duct were examined for the location of the tumor and its relation to adjacent structures. Wirsung duct was also opened if possible. Representative tissue samples were taken. The regional nodes were sampled also which were grouped as follows: Superior lymph nodes (superior to head and body of pancreas); inferior lymph nodes (inferior to head and body of pancreas); anterior lymph nodes (anterior pancreaticoduodenal, pyloric, and proximal mesenteric lymph nodes); posterior lymph nodes (posterior pancreaticoduodenal, common bile duct or pericholedochal and proximal mesenteric nodes) and splenic lymph nodes. WHO 2010 classification and TNM staging were used at final pathology reports.

Statistics

Chi-square tests were used to compare categorical variables. Independent t tests and Mann-Whitney tests were used to evaluate continuous variables. A P value of less than 0.05 was considered statistically significant.

Results

The mean \pm SD age was 64.55(19-82) years. There were 17 men and 20 women, 27 of patients presented with pancreatic cancer located to the head and uncinata process, 4 with distal common bile duct and duodenum, 6 with IPMN. Data concerning demographic properties of the patients and localization of tumors are reported in Table 1. The mean

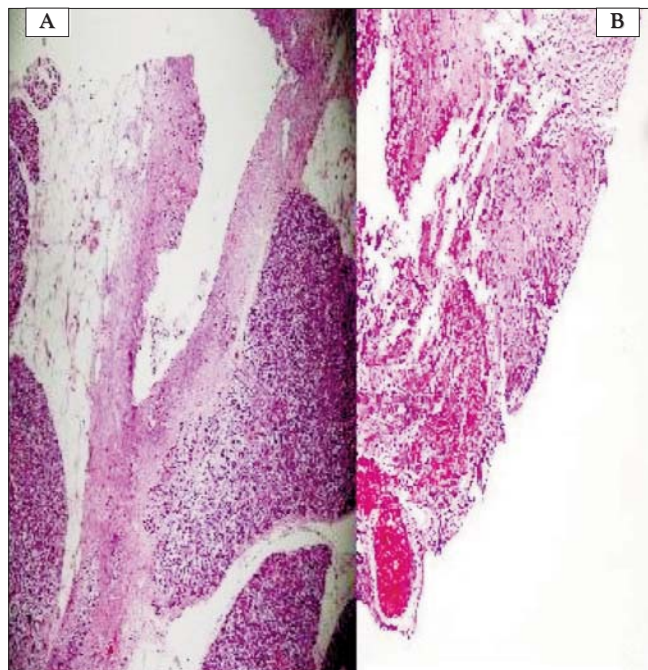


Figure 2. HEx40, Pancreatic neck margin; microscopical negative and tumor free (A), Retroperitoneal uncinata(SMA) margin; tumor so close to the surgical margin (B)

tumor size was 3.96(1.16-6.25) according to the final pathological examination. The average number of lymph nodes extracted was 18.52(9-45). All final pathologies were reported ductal adenocarcinoma of the pancreas and ampullary in which 6 arising from IPMN.

Frozen section analysis revealed in one patient with IPMN surgical margin positivity and the patient underwent total pancreatectomy. The final pathological reports were revealed no margin positivity for other patients.

Discussion

The incidence of pancreatic cancer has continued to increase dramatically worldwide. Although we can not report any statistical study data for our country, it is the fourth leading cause of cancer-related deaths in USA. Pancreatic cancer continues to portend a poor prognosis with a 5 years survival of less than 5% despite advances in diagnostic imaging, endoscopic diagnosis and staging, resection techniques, and perioperative care (11). Most of the pancreatic cancers involve the head of the pancreas with earlier presentation of jaundice due to obstruction of the pancreatobiliary system. Among the other tumors of the periampullary region, duodenal and distal common bile duct cancers also tend to present with jaundice in an earlier stage. Therefore, an effective surgical treatment which includes complete extirpation of the tumor with negative margins is going to be an important factor for long-term overall survival.

Operative resection remains the only potential cure for periampullary tumors. Also patients who underwent surgical resection have better survival. Unfortunately, even with curable complete resection, tumor tends to recur locally (12,13). The

impact of margin status in local recurrence has come under question. Raut and colleagues evaluated 360 consecutive patients in whom PD was performed for adenocarcinoma. Patients who underwent an R1 resection has a median overall survival of 21.5 months compared with 27.8 months in patients who underwent an R0 resection (14). Moreover, the recurrence in pancreatic cancers and periampullary tumors invading the pancreatic tissue after surgery depends on mostly to the surgical margin status and the tumor specific issues, especially infiltrating nature of the tumor and its aggressive tumor biology (14).

Preoperative, adequate and reliable examination with effective preoperative evaluation is thought to be essential to shorten the time and improve the quality of surgery. By that way, it is also possible to make a definitive surgical decision preoperatively (15). Radiological and endoscopic findings for local invasion with size of the tumor located in or invading to the pancreas should be taken into account for the decision of intraoperative frozen section analysis. In addition to determination of resection margin for the tumors located at the pancreas, frozen section analysis can be considered standard of care in distinguishing cystic neoplasm from pseudocyst and in confirming pancreatic duct margin as tumor-free in intraductal papillary mucinous neoplasms (6,9,10,16). Good surgical technique may eliminate the need for intraoperative frozen section analysis for the tumors without local invasive properties. In the present study, it was shown that positive pancreatic surgical margin could only be seen in 1/37 of the cases. Other margins were negative in all cases. However, it is better to perform the analysis to get negative margins in selected cases in which preoperative evaluation raises doubt.

In recent years, various investigations carried out to reduce the surgical margin positivity. Especially, the use of neoadjuvant treatment programs that employ gemcitabine-based chemotherapy regimens followed by chemoradiation increases the likelihood of subsequent margin-negative resection in borderline resectable pancreatic cancer (5). The impact of margin status study by frozen section analysis in patients who are radiologically operable without any doubt has not studied yet. There were many conflicting results with regard to the impact of surgical margin on overall survival of the tumors located at the periampullary region, especially pancreatic cancers. Although the deleterious effect of positive surgical margin on overall survival has been shown (4-7), others have had lack of such correlation (2,13,14). It was also shown that extended resections after positive surgical margin has had no effect on survival after pancreaticoduodenectomy (13). Therefore, effect of both positive surgical margin and extended resections after positive surgical margin on the surgical treatment of tumors of the periampullary region should be clarified by future studies.

In our study, pancreaticoduodenectomy with intraoperative frozen section analysis was performed in 37 consecutive radiologically proved operable pancreatic and periampullary cancer patients. Positive result for intraoperative frozen section analysis was seen only in one patient with an incidence of 2.7%. However, the incidence of positive surgical margin

during pancreaticoduodenectomy was reported to be up to 10-20% (5,7,13,17). It was thought that this low rate might be a cause of the accordance between preoperative evaluation for defining the size, geometry, and extent of the tumor, and surgical technique for increasing the possibility of R0 resection. With careful patient selection, state-of-the-art imaging, and proper surgical technique, R2 resections can be largely avoided.

In one of the patient the pathologic study revealed margin positivity incompatible with radiological findings. In the study 9 patients were reported to be borderline resectable by preoperative radiological study. But the frozen section analysis for these patients were negative for surgical margins. The only margin positive patient was the one with 4.5 cm tumor in diameter in pancreatic head.

Conclusion

In conclusion routine intraoperative biopsies are not necessary for pancreatic and periampullary tumors. But to determine the appropriate cut line and prevent recurrence, for patients with doubtful margins according complementary imaging modalities, an intraoperative frozen section histology analysis can be needed. This decision can be set according intraoperative surgical properties of the tumor, the experience of the surgeon, the size of the tumor and associated pancreatitis. Related to this subject further detailed studies should be done concerning the subgroups we mentioned above.

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