ORIGINAL ARTICLE

WHIPPLE RESECTION: CONCORDANCE BETWEEN FROZEN SECTION AND PERMANENT SECTION DIAGNOSIS OF SURGICAL MARGINS

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Background: Margin assessment is done in Whipple procedures which are usually performed to resect tumours of head of pancreas and ampullary/periampullary region. Aims and objective of the study are to determine the concordance between frozen sections (FS) and permanent sections (PS) of surgical margins in Whipple resections. **Methods:** It is a retrospective study, from January 2008 to January 2015 (07 years). It includes the specimen with malignancy in final report and for which FS of pancreatic and/or CBD margin(s) were requested. Data was retrieved from Laboratory information system (LIS) database. **Results:** Of the 41 bile duct margins in cases of ampullary tumours, 03 were positive on FS as well as PS, 35 were negative on FS as well as on PS. Results showed 100% sensitivity, 92.1% specificity, 50% PPV and 100% NPV. Results of 36 pancreatic margins in cases of ampullary showed 100% sensitivity, 97.1% specificity, 50% PPV and 100% NPV. In pancreatic carcinoma cases, none of CBD margins were reported as positive on FS, 02 margins reported as negative were found positive on PS, while 17 were negative on FS as well as PS. Results showed 100% specificity and 89.5% NPV. Of the 27 pancreatic margins tested in pancreatic tumours 100% sensitivity, 94.1% specificity, 88.9% PPV and 100% NPV was found. **Conclusion:** Factors such as absent prior tissue diagnosis and/or inflammatory processes make margin diagnosis difficult. However, a high concordance was observed between our FS and PS diagnosis.

Keywords: Frozen section; Pancreatic carcinoma; Pancreatic duct

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INTRODUCTION

Whipple and colleagues, in 1935, described the first pancreaticoduodenectomy (Whipple procedure) performed for a periampullary carcinoma.[1] It has undergone several modifications since then. It is performed for the resection of tumours involving head of pancreas, common bile duct (CBD), ampulla of Vater and duodenum. The pathologist is not usually part of the routine pre-operative workup. However, he/she plays an important role in guiding the management.[2]

In a Whipple resection specimen, there are different surgical margins that need to be assessed carefully for management to be successful. This assessment is arduous, as this is probably the only organ system, where the surgery in majority of the cases is performed without a prior tissue diagnosis.[2] Therefore; the pathologist has to comment on surgical margin(s) as positive or negative without the patients' actual lesional tissue previously available. Surgical margins requiring comment mostly include CBD and pancreatic margin(s), with occasional cases when uncinate margin and great vessels margin are also requested.[2] In addition, the surgeon may also send any suspicious lymph node to assess for extra-pancreatic spread. Sometimes it can be a very challenging task just to differentiate inflammatory from neoplastic cells.

Frozen section of the resection margins in a Whipple resection has an impact on disease recurrence; thus, affecting long-term prognosis and survival. However, the potential False positive (FP) might lead to extra-operative sectioning and release of pancreatic enzymes, while False negative (FN) can lead to recurrence.[2]The primary purpose of this consult is to guide immediate surgical management.[3] The Frozen section (FS) can thus provide the surgeons valuable information either to proceed or even terminate the procedure.[4] With respect to therapy pancreatic cancer patients having positive resection margin may benefit from the addition of radiotherapy to adjuvant chemotherapy. This further highlights the importance of margin assessment on FS and its confirmation on PS.[5]

On most occasions, CBD and pancreatic resection margins are evaluated.[2] Uncinate margin clearance is important prognostically, however, it is not routinely submitted for FS, as further surgical clearance cannot be performed even in the case of a positive margin.[2,6] This study has been performed to assess primarily the concordance of FS diagnosis with PS findings of margin status in Whipple resections. It is the first study on this aspect in our setup and will provide the baseline for further research in this aspect.

MATERIAL AND METHODS

It was a retrospective study, carried out at Histopathology department, Shifa International Hospital Islamabad, from January 2008 to January 2015 (seven years), after approval of institutional review board. All patients regardless of age or gender who underwent

Whipple resection, with primary carcinoma in pancreas or ampullary/periampullary region in the final report and for which FS of resection margin(s) was performed, were included. Cases without malignancy, metastatic tumours and tumours other than carcinoma of pancreas or ampulla were excluded. Non-probability, consecutive sampling was performed. There were a few cases in which only one margin was submitted for FS analysis. For histopathological analysis, College of American Pathology (CAP) cancer protocols were used as a guideline.[7] Data was retrieved from Lab information system (LIS) database. Preoperative tissue diagnosis was not available in any of these cases. The results of FS were recorded along with PS diagnosis of pancreatic duct and/or CBD margin(s). The surgical margins showing malignant, dysplastic or atypical cells were designated as positive. Margins without such cells were reported as negative for malignancy. In most cases, reports had been finalized by at least two experienced histopathologists. Statistical analysis of the data was done on SPSS version 23.0. Mean and standard deviation (SD) of quantitative variable which is age were calculated. Frequencies and percentages of qualitative variables, i.e., gender, FS and PS diagnosis of pancreatic duct and CBD were also calculated. The FS sensitivity, specificity, PPV, NPV and overall diagnostic accuracy were calculated, keeping PS diagnosis as the gold standard. Percent concordance between FS and PS were also calculated.

RESULTS

The FS of resection margins were requested for 70 Whipple resections during the study period. Cases for which Whipple resection was performed without malignancy in the final report e.g. pancreatitis were excluded while calculating final results making cases with tumour equal to 56. Thirty-four cases (48.5%) had ampullary/periampullary carcinoma and 22 cases (31.4%) had carcinoma of pancreas. Of the ampullary carcinoma cases 25 were males (73.5%) and 09 were females (26.4%). Among pancreatic carcinoma cases, 15 were males (68.2%) while 7 were females (31.8%). Mean age of 59.13±SD 11.44 (range of 31–85 years). Out of the ampullary carcinoma cases, total of 41 CBD margins and 36 pancreatic margins were tested, while in pancreatic tumour cases 19 CBD margins and 27 pancreatic margins were performed. On one hand, there were cases in which only one type of margin was requested for a given carcinoma while in others a particular margin was tested twice with further excision, after being given either positive or suspicious on first excision (re-excisions were, therefore, counted separately).

The results of 41 bile duct margins in cases of ampullary carcinomas were as follows: 3 margins were positive on FS as well as PS & 35 were negative on FS as well as on PS. In 3 cases, FS margin was reported as positive which turned out to be negative on PS. Results showed 100% sensitivity, 92.1% specificity, 50% PPV and 100% NPV. There were no false negatives. The results of 36 pancreatic margins in cases of ampullary carcinomas were as follows: 01 was positive on FS as well as PS, 01 positives on FS while negative on PS and 34 negatives on FS as well as PS. Results showed 100% sensitivity, 97.1% specificity, 50% PPV and 100% NPV. In pancreatic carcinoma cases, 19 CBD margins were evaluated and results were as follows: None were reported as positive on FS, 02 margins reported as negative were found positive on PS, while 17 were negative on FS as well as PS. Results showed 100% specificity and 89.5% NPV.

The results of 27 pancreatic margins tested in pancreatic tumour cases were as follows: 08 were positive on FS as well as PS, 01 was positive on FS while negative on PS and 18 were negative on FS as well as PS. There were no false negatives. Results showed 100% sensitivity, 94.1% specificity, 88.9% PPV and 100% NPV.

DISCUSSION

Interpretation of pancreatic pathology is tough even on PS and is further limited due to FS artefacts. Eighty to ninety percent accuracy rate in pancreatic lesions FS has been reported by large centers.[8] The microscopic positive margin rates are very variable and surgeon and pathologist both play an important role in the final margin status. According to some studies, overall low microscopic positive resection margin is probably the result of suboptimal evaluation by pathologists rather than good surgical technique.[9]

For many organ systems, the criteria of margin clearance are clearly identified. In case of pancreatic margin, the criterion of Hyland et al serves as a guideline to differentiate carcinoma from benign glands. They identified three features as ‘major criteria’ which are nuclear size variation of 4:1 or more, disorganized duct distribution and incomplete duct lumens. The ‘minor criteria’ enumerates more difficult to assess microscopic characteristics, including large irregular nucleoli, necrotic glandular debris, epithelial mitoses and perineural invasion.[2,11]

Additional features favouring carcinoma are disorganized stroma, single cell infiltration, cribriform glands and large nucleoli.[12] Non-neoplastic conditions such as chronic pancreatitis can potentially hamper the FS assessment of margin particularly when there is marked fibroblastic reaction, glandular atrophy and distortion of ductal system.[2,12,13] (Figure) The distorted glands can mimic adenocarcinoma of pancreas. Mucinous metaplasia and ductal epithelial hyperplasia, also commonly encountered in chronic pancreatitis can be wrongly interpreted as malignant.[2]

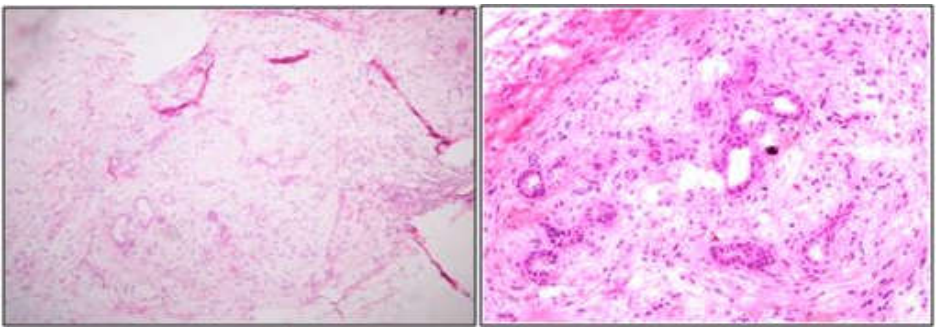

Figure-1: Frozen section of pancreatic margin showing lobular configuration of glands, exhibiting some degree of atrophy and fibrosis, at 20x (a). Later permanent section confirmed that margin is negative for malignancy, at 20x (b).

The CBD margin FS is frequently submitted as a separate piece of tissue, but is seldom positive. One may face difficulty in differentiating reactive glands from carcinoma. Perineural invasion can serve as a useful clue in such cases.[14]

There are a few centres in the world who have published comparisons of their FS and PS results in Whipple resection. WD Nelson *et al* published a retrospective analysis of 68 patients with pancreatic pathology comparing both the FS and PS results of resection margins. The study revealed that FS analysis for the determination of the final margin status was 33% sensitive, 100% specific with a PPV of 100%, and NPV of 97%, with an overall diagnostic accuracy of 97%. No FP was found.[15] The results of our pancreatic margins in cases of pancreatic tumours showed 100% sensitivity, 94.1% specificity, 88.9% PPV and 100% NPV. The specific data with respect to above mentioned margins from local institutes is not yet available, although findings from one centre are expected to be published soon.[16]

In a study by Porembka *et al*, frozen sections of resection margins were 100% accurate.[17] Badger S, *et al*, had documented that positivity of resection margin is related to tumour location, being highest for pancreatic carcinoma (54.5%) and lowest for periampullary carcinoma (9.6%).[18] We had 01 FP cases of pancreatic duct margin in cases of ampullary carcinoma and 01 FP in pancreatic tumour cases.

Kooby *et al*[19] performed analysis of FS and PS of pancreatic margin in 1399 Whipple resections for pancreatic carcinoma. Total of 1196 patients were negative while 131 patients remained positive even on re-excised margins. Pancreatic duct margin was negative in 23 (95.8%) cases and positive in 1 (4.2%) case of our Whipple resection for pancreatic carcinoma. Results remained unaltered on PS. However, we had a much smaller sample size as compared to them. Wilson *et al* evaluated 218 cases for pancreatic carcinoma and showed that a complete resection of margins was possible in additional 10 cases by FS evaluation.[20] There was no FP or FN result in their study. Our results, however, showed 01 false FP.

There are cases where a disagreement is found between the FS and PS diagnosis of either resection margins. In a five-year multi-institutional study by Raab SS *et al*, among the pancreatic cases, a discordance of 1.3% was found in which pancreas was evaluated for margin clearance.[21] In a study performed by WA Valerie *et al,* no discordance was found in cases of pancreas and no cases were deferred for PS.[22] Our study showed 01 FP in pancreatic tumour cases.

Regarding ampullary carcinoma no separate study regarding margin assessment was retrieved. In our study ampullary tumours showed 3 FP CBD margins and 01 FP pancreatic margin.

Despite the high concordance rates between the FS and PS analysis of margins and benefits of it, some recently published data has questioned the long-term benefit of this toilsome exercise. There is an emerging concept that margin clearance, particularly of pancreas, improves survival but not to a very significant extent.[9,19] This is particularly being evaluated in cases where an initial FS revealed a positive margin and subsequent FS were requested till margin clearance.[23,24]

CONCLUSION

The frozen section in Whipple resection specimen is difficult as usually no prior tissue diagnosis is available for comparison. Also, inflammatory process may mimic carcinoma due to distortion of architecture. Still, it is a good method to ensure negative margins and a useful guide for the surgeon to plan further management. A high concordance was observed between our frozen and permanent section diagnosis of pancreatic margin and

CBD margin; however, the survival benefit of this work remains to be evaluated and reported.

List of Abbreviations:

CAP: College of American Pathology, CBD: common bile duct, FP: false positive, FN: false negative, FS: frozen section, LIS: laboratory information system, NPV: negative predictive value, PPV: positive predictive value, PS: permanent section, SD: standard deviation, SPSS: Statistical Package for Social sciences.

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AUTHORS' CONTRIBUTION

MB: Conception and design of work, collection/interpretation of data, drafting & write-up, literature search, critical revision. HT: Design of work, collection/interpretation of data, write-up contribution, literature search, critical revision. NM: Design of work, data interpretation, critical revision and supervision at all stages and aspects of work.

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