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Adjuvant chemotherapy for resected invasive IPMN. Do we have evidence comparing with typical pancreatic cancer?

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Lecture :

1. Invasive Intraductal papillary mucinous neoplasm

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a grossly visible (typically>5mm) intraductal epithelial neoplasm producing mucin. According to the its origin in pancreatic ductal system, morphologically, IPMN can be divided into main-duct, branch duct or mixed type IPMN. Following pathological classification can be available after resection of IPMN;

- 8453/0 Intraductal papillary mucinous neoplasm with low-grade dysplasia
- 8453/2 Intraductal papillary mucinous neoplasm with high-grade dysplasia
- 8453/3 Intraductal papillary mucinous neoplasm associated with invasive carcinoma

Clinical significance of IPMN should be placed because it is precursor lesions for pancreatic ductal adenocarcinoma. The evolution of these lesions consist of progression through an adenoma-carcinoma sequence. Based on acquisition of driver mutations (notably KRAS and GNAS), subsequent transition through low grade to high grade dysplasia leads to invasive disease. Moreover, this precursor lesion can be detected early because it forms cystic nature on cross-sectional image, comparing other precursor lesion for usual pancreatic cancer, such as pancreatic intraepithelial neoplasia, allowing potential early identification of patients at risk of developing pancreatic cancer over time

Based on histological features and routine immunohistochemistry, there are distinct IPMN subtypes with different tumor characteristics; Gastric-type, Intestinal-type, Pancreatobiliary-type. The rare adenosquamous-subtype has also been reported for invasive IPMN. The oncocytic-type is now recognized as a distinct disease entity (ICD-O: 8555/2-3, 2019 WHO classification).

IPMN and invasive carcinoma can occur in the same pancreas. If the carcinoma arises in the area of IPMN, it is designated IPMN *associated with* invasive carcinoma; if the carcinoma is not contiguous with IPMN, it is designated IPMN *with concomitant* invasive carcinoma. Invasive IPMN can be divided into two distinct types; Colloid carcinoma vs. Tubular (ductal) adenocarcinoma. Colloid carcinoma is characterized by infiltrating epithelial cancer cells sparated by abundant stromal mucin, arising in association with intestinal-type IPMN. Tubular (ductal) adenocarcinoma is morphologically similar to conventional pancreatic ductal adenocarcinoma, arising in associated with either pancreatobiliary- and gastric-type IPMN. There are biological and prognostic differences between two types of invasive IPMN (Colloid carcinoma shows more favorable outcomes).

2. Different tumor biology of invasive IPMN comparing with conventional pancreatic ductal adenocarcinoma (PDAC)

Surgery is the standard of care for invasive IPMN. There are conflicting data whether or not inv-IPMN and PDAC have similar outcome. Some data suggest that invasive IPMN show similar outcome as the conventional counterpart, while other suggest a more favorable survival. Recent meta-analysis* investigating 14 studies showed improved 5-year overall survival for invasive IPMN compared to pancreatic cancer. Invasive IPMN was more often found at early stage of cancer (TNM-stage I) with lower rates of lymph node metastasis, however, data showed no survival difference for higher TNM stage. Recent Swedish nationwide register-based study* comparing 293 invasive IPMN and 1616 pancreatic ductal adenocarcinoma showed outcomes of resected invasive IPMN is more favorable in stage, N0-1, and M0 comparing to PDAC. However, in stage T2-4, and N2, survival is similar, and stage M1, even shorter survival was noted in invasive IPMN compared to PDAC.

In addition, from the view point of tumor recurrence, recent several studies* suggest invasive IPMN reveals different tumor biology from usual PDAC. Invasive IPMN was found to be associated with late recurrence. Liver metastasis constituted a minor part of recurrence, were generally part of multi-site recurrence. In addition, indolent lung metastasis was proportionally the most common recurrence site.

3. Current guideline regarding adjuvant treatment in treating resected pancreatic cancer

High level of evidences proved potential role of postoperative adjuvant chemotherapy (AC) in resected pancreatic cancer. Currently, in patients with good performance status, modified FOLFIRINOX or gemcitabine+ capecitabine are provided in potentially margin-negative resection*. However, considering only 5% of patients included in the studies, it is not surprising to give a question about potential role of AC for resected invasive IPMN.

4. Role of adjuvant chemotherapy in resected invasive IPMN

The role of adjuvant therapy for invasive IPMN has yet to be determined as the evidence from the wider literature is conflicting. Recent meta-analysis*, investigating 10 literatures, including 3252 patients, showed no statistically s significant difference in the OS was noted with AC in the entire cohort of invasive IPMN. However, a survival benefit was noted in a subgroup of patients with an aggressive disease phenotype; nodal involvement and advanced stage (≥ 2). However, recent our study* found that AC was associated with poor survival outcome of resected invasive IPMN. Especially, in stage I, survival of AC group was worse than surgery alone. Even in node positive group, survival outcome of AC group was lower than that of surgery alone group, suggesting further study should be performed to provide appropriate answer to following questions; Are chemotherapeutic agent used for PDAC appropriate in resected invasive IPMN? Who will benefit from AC? Considering the risk of systemic chemotherapy-related toxicity and medical cost, these issues need to be resolved. In this moment, the interim-result of recent Korean multicenter collaboration study regarding this issue will be introduced.

Summary of literatures investigating potential role of adjuvant treatment in resected IPMN

Author, Year	Study Period	N	Adjuvant treatment	Conclusion
Turrini, 2010	1989-2006	98	5-FU Gemcitabine 5-FU+RTx	No benefit
Swartz, 2010	1999-2004	70	5-FU+RTx	No benefit *Benefit in LN+ (p=0.044)
Alexander, 2010	1990-2005	49	5-FU+RTx	No Benefit *Benefit in higher stage, LN+
Worni, 2012	1988-2007	972	RTx	No benefit *Benefit in LN+, T3/4
Caponi, 2013	2005-2011	64	Gemcitabine Gemcitabine+RTx	Benefit
McMillan, 2015	1998-2010	1220	Regimen: NA RTx	Benefit
Duconseil, 2017	2005-2012	2005	Regimen: NA	Benefit *No benefit in LN-
Marchegiani, 2018	1990-2016	102	Gemcitabine Gemcitabine+Oxaliplatin 5-FU+Oxaliplatin RTx	No benefit *Benefit in N1, tubular carcinoma
Mungo, 2020	2006-2016	492	Regimen: NA RTx	Benefit in LN+ No benefit in LN-
Rodrigues, 2020	1993-2018	103	Gemcitabine, Gemcitabine+Capecitabine 5-FU Additional RTx	No benefit
Choi 2021	2001-2019	113	Gemcitabine, 5-FU, 5-FU+Cisplatin	No benefit
Kaiser, 2022	2002-2018	424	Regimen: NA	No benefit

5. Discussion

Following should be considered in the current controversial outcomes of postoperative adjuvant treatment in resected invasive IPMN.

- Published study is based on retrospective design and too old study period to apply in current clinical practice.
- No standardized treatment protocol.
- Completeness of adjuvant threat was not noted.
- Recently applied potent chemotherapeutic agent, such as FOLFIRINOX, was not evaluated.
- Invasive IPMN has disease-severity spectrum. According to this severity, long-term survival outcomes will be influenced.
- Considering different tumor biology according to subtypes of invasive IPMN, proportion of colloid vs tubular type of invasive IPMN in the study population might be selection bias.
- Some study demonstrated that adverse impact of adjuvant treatment in resected invasive IPMN, suggesting adjuvant treatment should be individualized.

Therefore, taking quite favorable long-term oncologic outcome of node negative invasive IPMN, in near future, patients with poor prognostic factors (such as lymph node metastasis, perineural invasion, margin positive disease) will be potential target group to be enrolled for multi-nations/multi-centers prospective randomized study investigating potential role of adjuvant treatment in resected invasive IPMN.

6. Reference

- WHO Classification of Tumours. 5th edition: Digestive system tumours. Edited by WHO Classificatin of tuours editorial borad
- Furukawa T, et al., Whole-exome sequencing uncovers frequent GNAS mutations in intraductal papillary mucinous neoplasms of the pancreas. Sci Rep 2011;161:1-7
- Mas L, et al., Intraductal Papillary Mucinous Carcinoma Versus Conventional Pancreatic Ductal Adenocarcinoma: A Comprehensive Review of Clinical-Pathological Features, Outcomes, and Molecular Insights. Int. J. Mol. Sci. 2021; 22:1-19
- M. Holmberg, et al., Outcome after surgery for invasive intraductal papillary mucinous neoplasia compared to conventional pancreatic ductal adenocarcinoma e A Swedish nationwide register-based study, Pancreatology, https://doi.org/10.1016/j.pan.2022.12.003
- Aronsson L, et al., Intraductal papillary mucinous carcinoma versus pancreatic ductal adenocarcinoma: A systematic review and meta-analysis Int J Surg 2019:71;91-99
- Capretti, et al., Invasive IPMN relapse later and more often in lungs in comparison to pancreatic ductal adenocarcinoma. Pancreatology 2022:33:782-788
- Gavazzi, et al., Pancreatic ductal adenocarcinoma and invasive intraductal papillary mucinous tumor: Different prognostic factors for different overall survival. Dig. & Liver Dis. 2022;54:826-833
- Taked, et al Survival comparison of invasive intraductal papillary mucinous neoplasm versus pancreatic ductal adenocarcinoma. Surgery. 2022;172:335-342
- Hughes D, et al., Determining the role of adjuvant therapy in Invasive Intraductal Papillary Mucinous Neoplasms; a systematic review and meta-analysis. Eur J Surg Oncol 2022;48:1567-1575
- Kaiser J, et al. IPMN-associated pancreatic cancer: Survival, prognostic staging and impact of adjuvant chemotherapy. Eur J Surg Oncol 2022;48:1309-1320
- Choi M, et al., Role of postoperative adjuvant therapy in resected invasive intraductal papillary mucinous neoplasm of the pancreas: A multicenter external validation. J Hepatobiliary Pancreat Sci. 2021;28: 671–679
- Springfeld C, et al Chemotherapy for pancreatic cancer. Presse Med. 2019; 48: e159–e174