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Symposium Summary

Pancreas club international joint symposium on pancreatic cancer 2012, Kyoto: down staging chemo±radiotherapy for borderline resectable pancreatic cancer

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This manuscript summarized one section out of the international symposium, Pancreatic Cancer 2012, which was held last October 4th through 6th in Kyoto (Japan) under the theme, "We are the Team: Opening the Door to the Next Step for Pancreatic Cancer Therapy." Borderline resectable pancreatic cancer (BRPC) is a specific clinical presentation with features in between those of resectable and locally advanced pancreatic cancers. The classification of pancreatic cancer is an important issue given that a cancer may look resectable but be high-risk for R1 or R2 resection. Considering that margin-negative resection is a fundamental requirement for curing pancreatic cancer, this issue is one of the most interesting to pancreatic surgeons. At Pancreatic Cancer 2012 in Kyoto, BRPC was also discussed at the Pancreatic Club International Joint Symposium. In this manuscript, the contents of the presented topics are briefly summarized to facilitate understanding of recent issues in managing BRPC. **(Korean J Hepatobiliary Pancreat Surg 2013;17:8-13)**

Key Words: Pancreatic cancer; Respectability; Chemoradiation therapy

INTRODUCTION

An international symposium, Pancreatic cancer 2012, was held last October 4th through 6th in Kyoto (Japan) under the theme, "We are the Team: Opening a Door to the Next Step for Pancreatic Cancer Therapy". As the catchphrase suggested, recent advances in basic research of pancreatic cancer/carcinogenesis, potential target for future therapy, diagnostic modalities, chemotherapy, chemoradiation therapy, immunotherapy, endoscopic intervention, and minimally invasive pancreatic surgery were all discussed in this meeting. There was only one large room available for oral plenary sessions at the conference center, thus every participant was able to contribute to the discussion of presentation topics and share the recent findings and opinions with others.

Borderline resectable pancreatic cancer (BRPC) is a specific clinical presentation with features in between those of resectable and locally advanced pancreatic cancer. The classification of pancreatic cancer is an important issue given that a cancer may look resectable but be high risk for R1 or R2 resection. Considering that margin-negative resection is a fundamental requirement for curing pancreatic cancer, this issue must be one of the most interesting to pancreatic surgeons. At Pancreatic Cancer 2012 in Kyoto, BRPC was also discussed at Pancreatic club International Joint Symposium. In this manuscript, the contents of presented topics are briefly summarized to facilitate understanding of recent issues in managing BRPC.

Vascular reconstruction during pancreatoduodenectomy for ductal adenocarcinoma of the pancreas improves resectablility but does not achieve patients cure

This session began with a presentation by Dr. Jean-Francois Gigot from Universite Catholique de Louvain (Belgium). Based on recent publication from his group,[1] he suggested the necessity of multidisciplinary approach to treat pancreatic cancer requiring combined vascular resection. In his talk, he reviewed their retrospective com-

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parative study between Group A (N=82, pancreaticoduodenectomy (PD) without vascular resection), Group B (N=67, PD with isolated vascular resection), and Group C (N=8, PD with arterial resection). Postoperative morbidity and mortality rates were reported to be similar in each group, however, R1 resection was significantly more frequent in Group B (42%) and C (50%) compared to Group A (13%, $p<0.001$). In addition, more advanced tumor conditions were related to Group B and C, including features such as lower Karnofsky index, a higher serum CA 19-9, large size, more advanced AJCC stage, and frequent location of the uncinate process of the pancreas. Ten-year overall and disease-free survival rates were significantly better in Group A (19%, and 20%, respectively) compared to Group B (2.8%, and 0%) and Group C (both 0%). Combined vascular resection and the presence of metastatic lymph node were determined to be independent prognostic factor on multivariate analysis, indicating that PD with vascular resection increased local resectability without additional perioperative morbidity and mortality, but was not associated with improved oncologic outcome. Especially, he claimed arterial resection should be regarded as contraindication due to high morbidity and poor survival outcome.

The result of that study are based on retrospective data collected during long-term follow-up period, and preoperative resectability was not exactly described in this study, however, it is thought that a significant portion of patients in Group B and C might had BRPC when considering the surgical outcomes of potentially resectable cancers with high risk of margin positivity. In addition, when we compared other studies reporting a lower incidence of lymph node metastasis in patients with pancreatic cancer who underwent pancreatectomy following neoadjuvant chemoradiation,[2-4] this paper seemed to be a good example of current oncologic problems of surgery as the first approach in BRPC cancer, supporting the potential application of neoadjuvant therapy in treating these patients.

Evolution towards chemo radiotherapy for BRPC, what promised to be best?

William Nealson from Vanderbilt University School of Medicine (USA) began his talk by asking the following questing; “Is there place for neoadjuvant therapy for BRPC? If so, chemotherapy alone or Chemoradiation therapy?” There are rationales for the use of neoadjuvant therapy in advanced pancreatic cancer, However, a recently published meta-analysis[5] evaluating the role of neoadjuvant therapy in advanced pancreatic cancer suggested (1) most available data provide a low level of evidence; (2) definitions of unresectable pancreatic cancer and BRPC are not consistent, or not clearly described; and (3) there is a general lack of stated criteria for resection after neoadjuvant therapy in most studies. All of these factors make it difficult to draw a meaningful conclusion about the therapeutic role of neoadjuvnat therapy in treating pancreatic cancer.

In addition, there are various types of intervention as neoadjuvant therapy, such as different radiotherapy techniques, chemotherapeutic agents, and treatment dose/schedule. The speaker specifically emphasized the fact that the role of radiotherapy in treating pancreatic cancer is still controversial. Considering the recurrence pattern of pancreatic cancer after both local radiotherapy and systemic therapy, he suggested chemotherapy would be ideal in treating pancreatic cancer. In fact, the addition of radiotherapy in an adjuvant setting was reported to decrease the local recurrence rate as low as 10%.[6-9] However, several randomized prospective study showed conflicting results, and no large randomized controlled study had been conducted on the use of neoadjuvant therapy in resectable pancreatic cancer. He concluded by reiterating that the routine use of neoadjuvant radiotherapy or chemoradiation therapy in treating pancreatic cancer remains controversial.[10]

Call for a standard set of definitions for BRPC

Dr. Howard Reber from University of California, Los Angeles (USA) practically focused on current controversial issue of the definition of BRPC. There are two available definition systems for BRPC, namely, the MDACC criteria and the AHPBA/SSO/SSAT criteria.[11,12] For a tumor abutting the SMV or portal vein, it is difficult to determine whether it as resectable pancreatic cancer or BRPC according to two different systems. In fact, some of these types of tumors may be regarded as potentially resectable according to the MDACC criteria, but BRPC in the AHPBA/SSO/SSAT definition system. However, he suggested pancreatic cancer with isolated venous vascular involvement may be potentially ‘resectable’ pancreatic cancer rather than BRPC for two primary reason. (1)

According to previous study of resectability based on CT criteria,[13] 85% of tumor abutting less than 25% of the SMV could be resected successfully and (2) In addition, PD with vascular resection can be safely performed with comparable oncologic outcome to potentially resectable pancreatic cancer based on the data published in *Borderline resectable pancreatic tumors: is there a need for further refinement of this stage?*[14]

He concluded that BRPC needs to be determined according to anatomic relationships between primary tumor and vascular structure. There are preliminary evidences in support of preoperative neoCRT for treating BRPC, however no phase III randomized controlled trail has been conducted to prove the role of neoCRT in BRPC. When considering the fact that current technique of PD with vascular resection does not compromise oncologic outcomes in well selected patients, defining preoperative resectability of tumors abutting the SMV as BRPC is still controversial issue. He suggested that more specific clinical study about isolated venous involvement of pancreatic cancer may be necessary for a more concrete definition of BRPC.

Role of the medical oncologist, criteria for down staging, role of CT imaging, success rates for resection, and survival results

In this session, different institutional experiences with a multidisciplinary approach to advanced pancreatic cancer were presented, and the audiences was instructed as to how the current concept of BRPC translates to clinical practices at UCLA (USA), Verona (Spain), and Mie (Japan) and had a chance to indirectly compare protocols at these institutions with their own.

UCLA experiences: The definition of BRPC in UCLA includes following anatomic components: (1) severe unilateral SMV/PV impingement; (2) short segment SMV occlusion; (3) tumor abuts SMA; (4) short segment encasement in GDA origin to HA; and (5) colon mesocolon invasion. Since early 1990s, preoperative neoCRT has been applied to these patients at UCLA with resection attempted later. Neoadjuvant radiotherapy was utilized in 25.6% of patients, and 74.4% of patients received neoadjuvant CTx without RTx. The response rate to neoCRT in BRPC was 25%. Even when there is no radiographic evidence of tumor progression on CT scan (vessels still looks involved), they attempted a radical pancreatectomy if patients performance status is good, and serum CA 19-9 drops dramatically after neoCRT. According to their experiences,[15] only three out of 49 patients showed true vascular invasion in those condition, suggesting that radiographic features such as distortion and narrowing of vessels after neoCRT turned out to be fibrotic changes in most cases. In addition, 40 patients could have R0 resection (85%) and 37 patients were shown to have no lymph node metastasis. Disease-free survival and overall disease specific survival rate were reported to be 42.2%, and 53.9%, respectively. He concluded by suggesting that vascular involvement of a pancreatic tumor may not only indicate locally advanced pancreatic cancer, but is also likely to reflect more extensive tumor biology, such as microscopic extension beyond the potential surgical margins. Therefore, preoperative neoCRT recommended to increase R0 rate and pN0 resection in BRPC. It is difficult to compare these results with those reported in the previous presentation from Belgium,[1] however, the audiences understand the rationales for use of neoCRT at these two different institutions.

From the view point of intention-to-treat in BRPC, it was not reported how many UCLA patients ultimately dropped out due to tumor progression during neoCRT, however proper selection of the patient who will benefit from a major pancreatectomy must be one potential role of neoCRT in BRPC, and the reported data seemed to support this. We are still waiting for the development of potent chemotherapy agents to increase the treatment effect and patient-selection power of neoCRT in advanced pancreatic cancer.

FOX chase experience: John Hoffman from Fox Chase Cancer Center (USA) presented the concept of multidisciplinary approach to pancreatic cancer based on their 25 years of experience. Considering poor oncologic outcomes regardless of the cancer stages, he suggested clinical trials-based approach according to clinical stage of pancreatic cancer would be optimal for managing these patients. For example, clinical trials need to evaluate the treatment efficacy of various postoperative therapeutic regimens in the setting of resectable pancreatic cancer. Various preoperative regimens, possibly including radiation therapy, also should be tested in BRPC. In addition, most recent developed agents need to be tested in un-

Table 1. Currently available grading systems of pathologic response to neoadjuvnat therapy

Authors, year	Grade	Description
Ishikawa et al., 1989[22]	1	＜33% severely degenerated cancer cells
	2	33-66% degenerated cancer cells
	3	≥66% degenerated cancer cells
Evans et al., 1992[23]	I	Characteristic cytologic changes of malignancy are present, but little (＜10%) or no tumor cell destruction is evident
	II	In addition to characteristic cytologic changes of malignancy, 10-90% of tumor cells are destroyed
	IIa	Destruction of 10-50% of tumor cells
	IIb	Destruction of 51-90% of tumor cells
	III	Few (＜10%) viable-appearing tumor eel Is are present
	IIIM	Sizable pools of mucin are present
	IV	No viable tumor cells are present
	IVM	Acellular pools of mucin are present
Pendurthi et al., 1996		＜80% fibrosis
		≥80% fibrosis
White et al., 2005[24]	*Necrosis*	*Residual Tumor Load* / *Fibrosis*
	Extensive	Large / Extensive
	Moderate	Moderate / Moderate
	Focal	Small / Mild
	Absent	Minimal
		None
Chun et al., 2011[16]	Minor	＜50% fibrosis relative to residual neoplastic cells
	Partial	50≤fibrosis＜95%
	Major	≥95% fibrosis
Hartman et al., 2012[25]	Poor	No definite evidence of treatment effect Expensive (90%) residual cancer Only minimal cytopathic effect and baseline fibrosis is present
	Minimal to moderate	-Residual tumor present, including small groups of cells/glands without evidence of cytopathic effect -Cells/glands outside the main fibrotic mass -And/or＜5% of the main fibrotic mass with cancer/glands, with or without cytopathic effect
	Marked	No residual tumor or rare, single cancer cells or small groups of cancer cells/glands with marked cytopathic effect present with a fibrotic stroma

resectable pancreatic cancer in well-designed clinical trials. He also emphasized the need for an assessment of the down-staging effect of neoCRT, and suggested the criteria for down-staging should be as objective as possible, and include both thin cut CT scans and serum CA 19-9 level. This group recently reviewed 135 consecutive patients treated with neoCRT followed by pancreatectomy for pancreatic cancer.[16] Pathologic response was defined as minor (＜50% fibrosis relative to residual neoplastic cells), partial (50-94% fibrosis), or major (95%≤fibrosis). They showed pathologic response was well correlated with R0 resection (p=0.019), negative lymph node status (p=0.006), and smaller tumor size (p=0.001). Median survival was significant different between partial response and major response (20 vs.66 months, p＜0.025; hazard ration, 2.26), concluding major pathologic response independently associated with prolonged survival. However, regarding role of CA 19-9 in determining treatment effect, Katz et al.[17] evaluated it as a marker of therapeutic response in pancreatic cancer with neoadjuvant therapy prior to planed surgical resection. They conclude, in spite of high positive predictive of CA 19-9, that the low negative predictive value compromised the clinical utility of CA 19-9 in assessing treatment effect of neoadjuvant therapy. In addition, there was no association between change in CA 19-9 and histopathologic response (p=0.74). The currently available grading system used to assess the treatment effect of neoadjuvant therapy in pancreatic cancer is summarized (Table 1).

The Mie University Experinece: Chemoradio-therapy followed by surgery for pancreatic ductal adenocarcinoma: ShujiIsalji from Mie University (Japan)

presented the experiences of 124 patients who underwent curative-intent resection following preoperative gemcitabine-CRT. This protocol for preoperative neoadjuvant therapy includes three- dimensional conformation radiotherapy (45 to 50.4 Gy/25 to 28 fractions) and weekly intravenous infusion of gemcitabine (800 mg/m^2 over 30 min) for 5 weeks with one- week break (Gem-CRT). According to NCCN guideline (2010),[11,18] 17 patients were classified as resectable (R), 54 as BRPC, and 53 as unresectable (UR). At the time of reassessment, distant metastasis was noted in 14% in R, 11% in BR, and 21% in UR, and tumor resection rate was 71.4% in R, 77.8% in BR, and 44.3% in UR. Margin-negative resection was reported to be 100% in R, 78.6% in BR, and 47.8% in UR. The three-year survival rate was significantly higher in 29 patients with CA 19-9 reduction rate greater than 50% in BRPC (42.8% vs. 9.7%, $p<0.0018$), and a reduction in CA 19-9 was reported to be an independent prognostic factor on multivariate analysis. The data seemed to indicate that the Mie protocol for R and BRPC is effective, and CA 19-9 reduction rate need to be considered an important clinical variable reflecting the down-staging effect of neoCRT.

Recently, this group also evaluated the relationship between intratumoral expression of human equilibrative nucleoside transporter (hENT1), the main gemcitabine transporter into the cell, and oncologic outcome of gemcitabine-based chemoradiation therapy in advanced pancreatic cancer patients.[19] They showed the hENT1 expression (positive in 39 and negative in 16 patients) was significantly associated with clinical efficacy (defined as reduction of CA 19-9 more than 50%, and partial response according to RECIST) of GEM-CRT. hENT1 expression group was found to have higher one-and three-year overall survival rates (82.9%, 39.5% vs. 42.9%, 14.3%, p=0.0037). Multivariate analysis revealed hENT1 expression and R0 resection were significant prognostic factors, suggesting the potential feasibility of an hENT1 expression-dependent personalized approach to advanced pancreatic cancer.[20,21]

CONCLUSION

After attending this symposium, the audiences could understand following issues;

1. In spite of current available surgical techniques, PD with vascular resection in advanced pancreatic cancer could increase resectability, but may not improve oncologic outcome.

2. Vascular involvement of pancreatic cancer may not only suggest locally advanced cancer but also extensive biologic properties beyond the potential surgical margin.

3. Preoperative neoadjuvant therapy, possibly including radiotherapy, is thought to be a reasonable approach in BRPC.

4. However, due to wide range of possible anatomic relationships between tumor and vessels, the definition of BRPC needs to be more standardized. According to current surgical techniques and the extant literatures, isolated venous involvement of pancreatic cancer may be regarded as resectable. A well-designed clinical trial will be required to further define the role of neoadjuvant treatment in this specific tumor condition.

5. Recently, many institutions have adopted pancreatectomy followed by neoadjuvant therapy for advanced pancreatic cancer.

In addition, it is thought that more evidence-based standardization of definition for BRPC, neoadjuvnat therapy protocol, operative records, and pathologic examination for histologic response is required to adequately address the role of pancreatectomy followed by neoadjuvnat therapy in treating BRPC.

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