ヒトを対象とする医学研究は、一般的に受け入れられた科学的原則に従い、科学的文献の十分な知識、他の関連した情報源及び十分な実験並びに適切な場合には動物実験に基づかなければならない。
環境に影響を及ぼすおそれのある研究を実施する際の取扱いには十分な配慮が必要であり、また研究に使用される動物の生活環境も配慮されなければならない。
すべてヒトを対象とする実験手続の計画及び作業内容は、実験計画書の中に明示されていなければならない。この計画書は、考察、論評、助言及び適切な場合には承認を得るために、特別に指名された倫理審査委員会に提出されなければならない。この委員会は、研究者、スポンサー及びそれ以外の不適当な影響を及ぼすすべてのものから独立であることを要する。この独立した委員会は、研究が行われる国の法律及び規制に適合していなければならない。委員会は進行中の実験をモニターする権利を有する。研究者は委員会に対し、モニターの情報、特にすべての重篤な有害事象について情報を報告する義務がある。研究者は、資金提供、スポンサー、研究関連組織との関わり、その他起こり得る利害の衝突及び被験者に対する報奨についても、審査のために委員会に報告しなければならない。
研究計画書は、必ず倫理的配慮に関する言明を含み、またこの宣言が言明する諸原則に従っていることを明示しなければならない。
ヒトを対象とする医学研究は、科学的な資格のある人によって、臨床的に有能な医療担当者の監督下においてのみ行われなければならない。被験者に対する責任は、常に医学的に資格のある人に所在し、被験者が同意を与えた場合でも、決してその被験者にはない。
ヒトを対象とするすべての医学研究プロジェクトは、被験者または第三者に対する予想し得る危険及び負担を、予見可能な利益と比較する注意深い評価が事前に行われていなければならない。このことは医学研究における健康なボランティアの参加を排除しない。すべての研究計画は一般に公開されていなければならない。
医師は、内在する危険が十分に評価され、しかもその危険を適切に管理できることが確信できない場合には、ヒトを対象とする医学研究に従事することを控えるべきである。医師は、利益よりも潜在する危険が高いと判断される場合、または有効かつ利益のある結果の決定的証拠が得られた場合には、すべての実験を中止しなければならない。
ヒトを対象とする医学研究は、その目的の重要性が研究に伴う被験者の危険と負担にまさる場合にのみ行われるべきである。これは、被験者が健康なボランティアである場合は特に重要である。
医学研究は、研究が行われる対象集団が、その研究の結果から利益を得られる相当な可能性がある場合にのみ正当とされる。
被験者はボランティアであり、かつ十分説明を受けた上でその研究プロジェクトに参加するものであることを要する。
被験者の完全無欠性を守る権利は常に尊重されることを要する。被験者のプライバシー、患者情報の機密性に対する注意及び被験者の身体的、精神的完全無欠性及びその人格に関する研究の影響を最小

限に留めるために、あらゆる予防手段が講じられなければならない。

ヒトを対象とする研究はすべて、それぞれの被験予定者に対して、目的、方法、資金源、起こり得る利害の衝突、研究者の関連組織との関わり、研究に参加することにより期待される利益及び起こり得る危険並びに必然的に伴う不快な状態について十分な説明がなされなければならない。対象者はいつでも報復なしに、この研究への参加を取りやめ、または参加の同意を撤回する権利を有することを知らされなければならない。対象者がこの情報を理解したことを確認した上で、医師は対象者の自由意志によるインフォームド･コンセントを、望ましくは文書で得なければならない。文書による同意を得ることができない場合には、その同意は正式な文書に記録され、証人によって証明されることを要する。

医師は、研究プロジェクトに関してインフォームド･コンセントを得る場合には、被験者が医師に依存した関係にあるか否か、または強制の下に同意するおそれがあるか否かについて、特に注意を払わなければならない。もしそのようなことがある場合には、インフォームド･コンセントは、よく内容を知り、その研究に従事しておらず、かつそうした関係からまったく独立した医師によって取得されなければならない。

法的無能力者、身体的若しくは精神的に同意ができない者、または法的に無能力な未成年者を研究対象とするときには、研究者は適用法の下で法的な資格のある代理人からインフォームド･コンセントを取得することを要する。これらのグループは、研究がグループ全体の健康を増進させるのに必要であり、かつこの研究が法的能力者では代替して行うことが不可能である場合に限って、研究対象に含めることができる。

未成年者のように法的無能力であるとみられる被験者が、研究参加についての決定に賛意を表することができる場合には、研究者は、法的な資格のある代理人からの同意のほかさらに未成年者の賛意を得ることを要する。

代理人の同意または事前の同意を含めて、同意を得ることができない個人被験者を対象とした研究は、インフォームド・コンセントの取得を妨げる身体的／精神的情況がその対象集団の必然的な特徴であるとすれば、その場合に限って行わなければならない。実験計画書の中には、審査委員会の検討と承認を得るために、インフォームド･コンセントを与えることができない状態にある被験者を対象にする明確な理由が述べられていなければならない。その計画書には、本人あるいは法的な資格のある代理人から、引き続き研究に参加する同意をできるだけ早く得ることが明示されていなければならない。

著者及び発行者は倫理的な義務を負っている。研究結果の刊行に際し、研究者は結果の正確さを保つよう義務づけられている。ネガティブな結果もポジティブな結果と同様に、刊行または他の方法で公表利用されなければならない。この刊行物中には、資金提供の財源、関連組織との関わり及び可能性のあるすべての利害関係の衝突が明示されていなければならない。この宣言が策定した原則に沿わない実験報告書は、公刊のために受理されてはならない。

C. メディカル·ケアと結びついた医学研究のための追加原則

医師が医学研究をメディカル·ケアと結びつけることができるのは、その研究が予防、診断または治療上価値があり得るとして正当であるとされる範囲に限られる。医学研究がメディカル·ケアと結びつく場合には、被験者である患者を守るためにさらなる基準が適用される。

新しい方法の利益、危険、負担及び有効性は、現在最善とされている予防、診断及び治療方法と比較考量されなければならない。ただし、証明された予防、診断及び治療方法が存在しない場合の研究において、プラシーボまたは治療しないことの選択を排除するものではない。

研究終了後、研究に参加したすべての患者は、その研究によって最善と証明された予防、診断及び治療方法を利用できることが保障されなければならない。

医師はケアのどの部分が研究に関連しているかを患者に十分説明しなければならない。患者の研究参加の拒否が、患者と医師の関係を断じて妨げるべきではない。

患者治療の際に、証明された予防、診断及び治療方法が存在しないときまたは効果がないとされているときに、その患者からインフォームド・コンセントを得た医師は、まだ証明されていないまたは新しい予防、診断及び治療方法が、生命を救い、健康を回復し、あるいは苦痛を緩和する望みがあると判断した場合には、それらの方法を利用する自由があるというべきである。可能であれば、これらの方法は、その安全性と有効性を評価するために計画された研究の対象とされるべきである。すべての例において、新しい情報は記録され、また適切な場合には、刊行されなければならない。この宣言の他の関連するガイドラインは、この項においても遵守されなければならない。

# 4．研究成果の刊行物

# Influence of preoperative anti-cancer therapy on resectability and perioperative outcomes in patients with pancreatic cancer: Project study by the Japanese Society of Hepato-Biliary-Pancreatic Surgery

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**Key words:** Pancreatic cancer, Neoadjuvant, Surgery, Resectability, Perioperative outcome

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Abstract

**Background/Purpose:** Little is known about the effects of neoadjuvant therapy on outcomes in patients with pancreatic cancer. This study evaluated the effects of neoadjuvant therapy on resectability and perioperative outcomes.

**Methods:** A total of 992 patients were enrolled, with 971 deemed eligible. Of these, 582 had resectable tumors and 389 had borderline resectable tumors, and 388 patients received neoadjuvant therapy. Demographic characteristics and peri- and postoperative parameters were assessed by a questionnaire survey.

**Results:** The R0 rate was significantly higher in patients with resectable tumors who received neoadjuvant therapy than in those who underwent surgery first, but no significant difference was noted in patients with borderline resectable tumors. Operation time was significantly longer and blood loss was significantly greater in patients who received neoadjuvant therapy than in those who underwent surgery first, but there were no significant differences in specific complications and mortality rates. The node positivity rate was significantly lower in the neoadjuvant than in the surgery-first group, indicating that the former had significantly lower stage tumors.

**Conclusions:** Neoadjuvant therapy may not increase the mortality and morbidity rate and may be able to increase the chance for curative resection against resectable tumor.

Introduction

Patients with pancreatic cancer have a dismal prognosis, even when tumors are resectable. Both local and systemic recurrences are common after curative (R0) resection, and long-term survival rates are low. The standard treatment for patients with resectable pancreatic cancer is surgery followed by adjuvant chemotherapy [1-5)], but the 2-year postoperative survival rate remains below 50% [3-5].

Neoadjuvant therapy has been used as an alternative approach in other types of cancer, including breast and esophageal cancers. In breast cancer patients, neoadjuvant chemotherapy has been shown to effectively reduce tumor burden in the breast and axilla without compromising survival [6]. In esophageal cancer patients, preoperative chemotherapy was found to result in longer overall survival than postoperative chemotherapy, and therefore, neoadjuvant chemotherapy became the standard treatment strategy for patients with resectable esophageal cancer [7]. Although reports from single institutions and prospective phase II trials found that neoadjuvant treatment had survival benefits in patients with pancreatic cancer [8-11], no large randomized trials have been performed yet to confirm these results.

The neoadjuvant strategy is subject to 2 major hypothetical risks: 1) possible increases in operative morbidity and mortality and 2) the possibility that the disease may metastasize or become unresectable during the course of neoadjuvant chemotherapy [12]. The resectability and perioperative outcomes in patients with resectable and borderline resectable pancreatic cancer could not be assessed in prospective trials of adjuvant chemotherapy [3-5] because these trials did not include patients with metastases detected intraoperatively or soon after surgery, patients who died due to surgical complications, and those who experienced severe morbidity and delayed surgical recovery. A survey is required to evaluate the effects of neoadjuvant treatment in patients intended for pancreatic resection.

Therefore, to clarify this situation, the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHPBS) surveyed high-volume centers throughout Japan that had experience with neoadjuvant therapy to evaluate the influence of neoadjuvant therapy on resectability and perioperative outcomes.

## Methods

A questionnaire was sent to all patients with pancreatic cancer who were scheduled to undergo resection with curative intent between January 2007 and December 2009 at the 17 high-volume centers participating in the JSHPBS study. This study was approved by the institutional review board of Tohoku University.

The eligibility of this study was invasive ductal adenocarcinoma of the pancreas, which was resectable or borderline resectable intending to surgery. Other types of histology were ineligible, such as acinar cell carcinoma, neuroendocrine tumor, cystic neoplasms. The demographic and clinical characteristics evaluated included patient age, gender, body mass index (BMI), comorbid illness, preoperative tumor staging and resectability [13], and pre- and post-treatment levels of tumor markers. Preoperative treatment data included chemotherapeutic agents; whether or not radiation was administered; the planned and administered doses of both; and adverse events (AEs), both hematological and non-hematological, during preoperative treatment, as assessed by Common Terminology Criteria for Adverse Events ver3.0 [14]. Operative findings included macroscopic tumor stage and intra-operative parameters, such as blood loss, duration of operation, and blood transfusion requirements. Pathological findings included pathological staging, residual tumor status, the effect of preoperative treatment, and intraoperative mortality. Postoperative data included postoperative complications such as pancreatic fistula, defined according to ISGPF (postoperative pancreatic fistula: an international study group) criteria [15]; delayed gastric emptying, as defined by the ISGPS [16]; other non-abdominal complications; postoperative hospital stay; and types of adjuvant treatment.

Of the 992 patients enrolled, 21 were excluded: 14 with primary unresectable tumors, 6 who were not assessed for resectablity, and 1 with no clinical records. Thus, 971 patients were included.

Primary outcomes included resectability and perioperative morbidity and mortality. To minimizing biases associated tumor stage, all eligible patients were stratified according to the presence of resectable or borderline resectable tumors, as defined by the National Comprehensive Cancer Network (Figure 1). The tumor without any abutment of major vessel including portal vein/supeior mesenteric vein (PV/SMV), superior mesenteric artery, hepatic artery, celiac artery was categorized in resectable. The tumor with impingement of PV/SMV but reconstructable and/or major arterial abutment within 180 degree, which was considered to be separable at surgery was categorized in borderline. The indication of resection depended on each institution surveyed. Assessment of resectability was answered by questionnaire survey. Resectability and R0-resectability were calculated on an intention-to-treat basis, and therefore, patients who did not undergo surgery for any reason were included. Perioperative morbidity and mortality of patients receiving neoadjuvant therapy (neoadjuvant patients) and those undergoing surgery without neoadjuvant therapy (surgery-first patients) were compared separately in subgroups of patients with resectable and borderline resectable tumors, because of differences in operative procedures, such as major vessel resection (Tables 4 and 5). The efficacy of neoadjuvant therapy could be assessed radiologically in 325 of the 389 patients (83.5%). Best percentage change from baseline in the size of the primary tumor was shown by waterfall plot analysis (Figure 2).

Statistics:

Continuous variables were expressed as median and range. Between group differences in patient characteristics and perioperative and postoperative factors were compared using chi-square tests, Fisher's exact test, and Mann Whitney's *U* test, as appropriate. Statistical significance was defined as $P < 0.05$.

Results

Patient characteristics

Of the 971 included patients, 582 had resectable and 389 had borderline resectable tumors. The clinical characteristics of these patients are shown in Table 1. Patients with borderline resectable tumors were significantly younger ($p < 0.001$) and had jaundice followed by biliary drainage more frequently ($p < 0.001$) than those with resectable disease. Pre-treatment serum concentrations of tumor markers were significantly higher in patients with borderline resectable tumors than in those with resectable tumors. Medical history did not differ significantly, except that previously malignancies were significantly more frequent in the resectable group ($p = 0.012$). In each subgroup, of patients with resectable and borderline resectable tumors, there were no statistically significant differences in age, sex, presence of jaundice, and serum tumor markers between patients who received neoadjuvant treatment and those who underwent surgery first (data not shown).

Neoadjuvant therapy

A total of 388 patients (40%) received neoadjuvant treatment, including 254 who received radiotherapy or chemoradiotherapy and 115 who received systemic chemotherapy. Types of therapy and agents are summarized in Table 2. Neoadjuvant treatment was significantly more common in patients with borderline resectable than in those with resectable cancers (52% vs. 32%, $p < 0.0001$). Gemcitabine or a gemcitabine-based regimen was the most frequently provided for chemoradiotherapy and systemic chemotherapy. In regard to neoadjuvant radiotherapy, the duration of preoperative therapy in resectable group was significantly longer than that in borderline group (99.5 days vs. 82 days). Whereas in regard to neoadjuvant chemotherapy, the duration in resectable group was significantly shorter than that in borderline group (28 days vs. 81.5 days).

Feasibility and efficacy of neoadjuvant therapy

Hematological and non-hematological AEs during neoadjuvant therapy are shown in Table 2. There were no neoadjuvant therapy-related deaths. Neutropenia and leukocytopenia occurred in more than half of the patients who received neoadjuvant therapy. Any grade leukocytopenia ($p = 0.0003$), anemia ($p < 0.0001$), fatigue ($p = 0.048$), nausea/vomiting ($p = 0.0006$), and anorexia ($p = 0.01$) were significantly more frequent in patients receiving chemoradiotherapy than systemic chemotherapy. Grade 3/4 neutropenia was significantly more frequent in patients receiving chemotherapy ($p = 0.0164$), whereas grade 3/4 leukocytopenia was significantly more frequent in patients receiving chemoradiotherapy ($p = 0.0007$). There were significant differences in any other AE.

Radiological tumor response to neoadjuvant therapy was assessed by tumor reduction rate, shown by waterfall chart analysis (Figure 2). The median tumor reduction rate was 6.3% (range, -45.2%–93.9%). According to Response Evaluation Criteria In Solid Tumors (RECIST) guidelines, 16% of patients showed a partial response, 80% had stable disease, and 4% had progressive disease (PD); none had a complete response to neoadjuvant therapy. Responses to neoadjuvant therapy were similar in patients with resectable and borderline resectable tumors ($p = 0.14$).

Resectability

Of the 388 patients who received neoadjuvant treatment, 25, including 8 with resectable and 17 with borderline resectable tumors, did not undergo surgery, including 21 (84%) with PD and 1 with an AE during preoperative treatment. Of the 582 patients with resectable disease, 397 were scheduled for surgery-first, and, of these, 375 (94.5%) underwent resection. Similarly, of the 185 patients with resectable disease who received neoadjuvant therapy, 171 (92.4%) underwent resection ($p = 0.34$). R0 resection was performed on 305 patients in the surgery-first group and 164 in the neoadjuvant group. The R0 rate was significantly higher in the neoadjuvant than in the surgery-first group, both by on-treatment ($p < 0.0001$) and intention to treat ($p = 0.0003$) analysis (Table 4A). Of the 389 patients with borderline resectable disease, 186 were scheduled to undergo surgery first, and, of these, 156 (83.9%) underwent resection. Similarly, of the 203 patients with borderline resectable

disease who received neoadjuvant treatment, 156 (77.8%) underwent resection (p = 0.16). Curability assessment showed no significant differences between the 2 groups, both by on treatment and intention to treat analysis (Table 4B).

Perioperative outcomes

Perioperative morbidity and mortality were evaluated in the 870 patients who underwent pancreatic resection, after excluding the 76 patients who underwent exploratory or bypass surgery. Of these 870 patients, 16 (1.8%) died. In the 546 patients with resectable tumors, there were no significant differences between the neoadjuvant and surgery-first groups in the proportions that underwent various operative procedures or combined resection of major vessels. Operation time was significantly longer (p = 0.0001) and blood loss was significantly greater (p = 0.0059) in the neoadjuvant than in the surgery-first group. There were 6 operative deaths (1.6%) in the surgery-first group and 1 (0.6%) in the neoadjuvant group (p = 0.44). Median postoperative hospital stay was significantly longer (p = 0.0020), and morbidity rate was slightly but not significantly higher (p = 0.084) in the neoadjuvant than in the surgery-first group. There were no significant differences in specific postoperative complications, including pancreatic fistula and delayed gastric emptying, as well as in rates of severe complications and reoperation (Table 5).

Of the 314 patients who underwent resection for borderline resectable tumors, those who received neoadjuvant treatment were significantly more likely to undergo resection of the pancreas head (p = 0.0026) and portal vein (p = 0.0018) than those who underwent surgery first. Operation time was significantly longer in the neoadjuvant than in the surgery-first group (p = 0.0005), but there were no between group differences in blood loss (p = 0.16), mortality (p = 0.17), and hospital stay (p = 0.50) (Table 6). Morbidity tended to be less frequent in the neoadjuvant group than in the surgery-first group (p = 0.057). In contrast to patients with resectable tumors, the postoperative pancreatic fistula (POPF) rates in patients with borderline resectable tumors were significantly lower in the neoadjuvant group than in the surgery-first group, both for all grades (p = 0.022) and grade B/C (p =

0.015). Fluid collection was significantly more frequent in the neoadjuvant than in the surgery-first group (p = 0.016). Other specific complications and their severity were similar in these 2 groups (Table 6). In resectable group with neoadjuvant therapy followed by resection, the proportion of delayed gastric emptying (DGE) in chemoradiotherapy was significantly higher than that in chemotherapy (21.6% vs. 10.1%, p=0.0015). The proportion of other post-operative complications as well as severity of complications and reoperation listed in Table 5 was similar in both treatment modalities. In borderline group with neoadjuvant therapy followed by resection, the proportion of grade B/C POPF in chemotherapy was slightly, but not statistically significant, higher than that in chemoradiotherapy (10.5% vs. 4.8%, p=0.092). The proportion of other post-operative complications as well as severity of complications and reoperation listed in Table 6 was similar in both treatment modalities.

Histological staging;

Table 7 shows a univariate comparison of histological staging according to the American Joint Committee on Cancer (AJCC). Of patients with resectable tumors, those who received neoadjuvant therapy had a lower T grade of the primary tumor than those who underwent surgery first (p = 0.033). Moreover, the percentage of patients with lymph node-positive tumors was significantly lower in the neoadjuvant than in the surgery-first group (30.6% vs 55.2%, p < 0.0001), resulting in a significantly lower stage in the former (p < 0.0001). In patients with borderline resectable tumors, those who received neoadjuvant treatment had a significantly lower grade of the primary tumor (p = 0.042), a significantly lower rate of node-positive tumors (44.3% vs 74.8%, p < 0.0001), and a significantly lower tumor stage (p < 0.0001).

Discussion

This survey clarified the feasibility, efficacy, and perioperative outcomes including resectability following neoadjuvant therapy in patients with pancreatic cancer. Adjuvant chemotherapy with gemcitabine is a standard therapy following resection for pancreatic cancer and significantly enhances recurrence-free and overall survival compared with surgery alone, with a median overall survival of almost 2 years after surgery [3-5]. However, this approach of surgery followed by adjuvant therapy cannot be offered to a significant proportion of patients with pancreatic cancer because of risks of surgical morbidity and the presence of unresectable disease at laparotomy. In contrast, almost all patients can receive neoadjuvant therapy before surgery [17,18].

A major concern in treating these patients with neoadjuvant therapy is the risks of operative morbidity and mortality. Although several small prospective studies have demonstrated the feasibility of this approach [10,11,19], this has not been confirmed because of the small sample sizes. Several nationwide surveys [20,21] and systematic reviews and meta-analyses [22,23] indicated that this strategy was feasible in larger numbers of patients, but could not quantify the data. Only 1 systematic review showed the rate of surgical morbidity and mortality after neoadjuvant therapy [24]. We found that neoadjuvant treatment did not significantly increase perioperative mortality and morbidity rates, including pancreatic fistula and delayed gastric emptying, indicating that neoadjuvant treatment was a feasible strategy in patients with pancreatic cancer. Neoadjuvant therapy, however, resulted in significantly longer operation times and postoperative hospital stay, as well as higher rates of grade 3/4 hematological toxicities. Nevertheless, these preoperative toxicities were manageable, with <0.5% of patients becoming ineligible for surgery.

Another concern associated with the neoadjuvant strategy is a possible decrease in tumor resectability due to tumor progression during preoperative treatment. A meta-analysis showed that, of patients with resectable tumors, 73.6% to 82.9% remained resectable after neoadjuvant therapy [17,24], findings similar to those in patients scheduled for primary resection and adjuvant therapy. We found that neoadjuvant therapy did not decrease tumor resectability, both in patients with resectable and borderline resectable pancreatic cancers. Intention-to-treat analysis showed that, in resectable tumors, the curability (R0 resection rate) was improved after neoadjuvant treatment. Radiologically,

90% of patients who received neoadjuvant therapy showed lack of tumor progression or tumor shrinkage, with only 10% showing tumor progression, suggesting that neoadjuvant treatment increased the likelihood of curative resection. These advantages of neoadjuvant therapy, however, were not observed in patients with borderline resectable disease, and resectability and R0 resectability were similar in the neoadjuvant and surgery-first groups. The incidence of nodal involvement was significantly lower in the neoadjuvant than in the surgery-first group. Neoadjuvant therapy has been reported to reduce the number of lymph node metastases [25,26], suggesting that the main effect of neoadjuvant therapy is to reduce peripancreatic lymph node positivity rather than the size of primary tumors. Since nodal involvement is one of the most significant predictors of patient survival [27,28], neoadjuvant therapy may have a survival benefit following resection of pancreatic cancer.

Although the number of patients receiving neoadjuvant therapy is the largest to date, questionnaire surveys have limitations. Data were collected from the various treatment centers retrospectively, not prospectively. In addition, there was significant inter-center heterogeneity in eligibility criteria for neoadjuvant treatment, neoadjuvant regimens, radiologic and intraoperative indications for resection, and postoperative therapy regimens. This heterogeneity may have introduced selection biases, preventing definite conclusions. Prospectively designed trials with adequate numbers of patients are required to determine the feasibility and efficacy of neoadjuvant treatment in patients with pancreatic cancer. This survey analyzing the effects of neoadjuvant treatment on resectablity and perioperative outcomes in patients with pancreatic cancer could not determine the impact of treatment on survival. However, several studies have reported that neoadjuvant therapy had survival benefits in patients with resectable or borderline resectable pancreatic cancer [11,17,21,22,24]. These suggest the need for prospective randomized studies to clarify the effects on survival of neoadjuvant therapy compared with the standard surgery-first strategy, in patients with pancreatic cancer [12,18]. In conclusion neoadjuvant therapy may not increase the mortality and morbidity rate, and may be able to increase the chance for curative resection especially against resectable tumor.

References

1.Neoptolemos JP, Dunn JA, Stocken DD, Almond J, Link K, Beger H, et al; European Study Group for Pancreatic Cancer. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet 2001;358:1576–85.

2. Stocken DD, B of randomised adjuvant therapy trials for pancreatic cancet al; Pancreatic Cancer Meta-analysis Group. Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. Br J Cancer 2005;92:1372–81.

3. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA 2007;297:267–77.

4. Ueno H, Kosuge T, Matsuyama Y, Yamamoto J, Nakao A, Egawa S, et al. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. Br J Cancer 2009;101:908–15.

5. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, et al; European Study Group for Pancreatic Cancer. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA 2010;304:1073–81.

6. Kaufmann M, Morrow M, von Minckwitz G, Harris JR; Biedenkopf Expert Panel Members. Locoregional treatment of primary breast cancer: consensus recommendations from an International Expert Panel. Cancer 2010;116:1184–91.

7. Ando N, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol 2012;19:68–74.

8. Palmer DH, Stocken DD, Hewitt H, Markham CE, Hassan AB, Johnson PJ, et al. A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: gemcitabine alone versus gemcitabine combined with cisplatin. Ann Surg Oncol 2007;14:2088–96.

9. Heinrich S, Pestalozzi BC, Sch and cisplatin for resectable adenocarciet al. Prospective phase II trial of neoadjuvant chemotherapy with gemcitabine and cisplatin for resectable adenocarcinoma of the pancreatic head. J Clin Oncol 2008;26:2526–31.

10. Varadhachary GR, Wolff RA, Crane CH, Sun CC, Lee JE, Pisters PW, et al. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. J Clin Oncol 2008;26:3487–95.

11. Evans DB, Varadhachary GR, Crane CH, Sun CC, Lee JE, Pisters PW, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. J Clin Oncol 2008;26:3496–502.

12. Reni M. Neoadjuvant treatment for resectable pancreatic cancer: time for phase III testing? World J Gastroenterol 2010;16:4883–7.

13. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Pancreatic adenocarcinoma, version 2.2010. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

14. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, (http://ctep.cancer.gov)

15. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al; International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138:8–13.

16. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007;142:761–8.

17. Andriulli A, Festa V, Botteri E, Valvano MR, Koch M, Bassi C, et al. Neoadjuvant/preoperative gemcitabine for patients with localized pancreatic cancer: a meta-analysis of prospective studies. Ann Surg Oncol 2012;19:1644–62.