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Original Research

Evaluation of the prognostic value of the new AJCC 8th edition staging system for patients with pancreatic adenocarcinoma; a need to subclassify stage III?

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Abstract ***Background:*** There have been several proposed changes for the 8th edition of the American Joint Commission on Cancer (AJCC) for pancreatic adenocarcinoma. The aim of this study was to evaluate the prognostic value of the new staging system for patients with pancreatic adenocarcinoma, especially in stage III patients.
Methods: We analysed the data of patients newly diagnosed with pancreatic adenocarcinoma between 2008 and 2016 at our hospital. Patients were staged according to 7th edition AJCC criteria, as well as the new 8th edition staging system. The pathologic stage was used in the surgical cases, and the clinical stage, determined by radiographic findings, was used in the unresectable cases.
Results: Five hundred two patients were identified who met the inclusion criteria. In node-negative patients, there were no significant differences in survival among T 1, 2 and 3 groups according to the 8th edition. The survival rates of patients with N1 (1–3 positive nodes) and N2 (≥4 positive nodes) disease, according to 8th edition, were significantly different ($p < 0.001$). Although N2 and T4 patients are both stage III according to the new staging system, N2 patients had a better survival rate than T4 patients ($p = 0.038$). The new staging system stratifies patients more evenly across stages without sacrificing the prognostic accuracy.

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Conclusions: The AJCC 8th edition has some advantages over the previous version. However, patients with N2 and T4, who have been integrated into stage III, showed different treatment modalities and prognoses, and we proposed dividing stage III into IIIA (T1-3N2M0) and IIIB ($T4N_{any}M0$).

1. Introduction

Pancreatic cancer is the seventh leading cause of cancer-related deaths across both genders worldwide [1]. Despite advances in multimodality treatment, pancreatic cancer remains a devastating malignancy with a dismal 5-year survival of about 5% [2]. For the proper treatment of pancreatic cancer, accurate staging systems for prognostic assessment are essential.

There have been several proposed changes for the new 8th edition of the American Joint Commission on Cancer (AJCC) for pancreatic adenocarcinoma [3]. Two major modifications were made from the previous 7th edition staging system. First, T3 categories are based on the size of the invasive tumour; 'extension beyond the pancreas' is no longer part of the definition, and T3 tumours are now defined as those larger than 4 cm. Extrapancreatic extension is difficult to determine and may not be reproducible between pathologists because the pancreas does not have a capsule, and the distinction between the pancreas and extrapancreatic tissue is often obscured by fibrosis [4,5]. Size-based definitions can be more objective. Second, previous node-positive N1 has been subdivided into N1 (1–3 positive regional lymph nodes) and N2 (≥4 positive regional lymph nodes). Recent studies have shown that not only the presence of nodal involvement but also the number of positive lymph nodes predicts survival outcomes [6–8].

In addition to these two major changes, another new feature of the 8th edition is that N2 is classified as stage III cancer, regardless of T staging. Previously, stage III pancreatic cancer included only T4 tumours involving the major arteries, and most of the cases were unresectable. However, according to the new staging system, both patients who were diagnosed with N2 after surgery and those who could not undergo surgery because of major vascular invasion (T4) are all included in stage III.

The AJCC 8th edition did not provide any rationale for N2 to be included into stage III cancer. Subsequent validation studies using the Surveillance, Epidemiology, and End Results (SEER) database of the US National Cancer Institute have been mainly performed only in the operative group, but not in the whole group of stage III patients, according to AJCC 8th edition [9–11].

Therefore, we aimed to evaluate the prognostic value of the new AJCC 8th edition for pancreatic adenocarcinoma and to investigate whether stage III cancer has been properly categorised.

2. Materials and methods

2.1. Patients and data collection

Patients newly diagnosed with pancreatic cancer between 2008 and 2016 at Seoul St. Mary's Hospital, Seoul, Korea, were retrospectively analysed. Patients with pathologically confirmed pancreatic adenocarcinoma or exocrine carcinoma were included in this study. Patients with unresectable pancreatic cancer underwent endoscopic ultrasound–guided fine needle biopsy for the primary lesion and/or percutaneous biopsy for metastatic lesions such as liver metastasis or carcinomatosis peritonei. Patients who failed to obtain adequate tissue were received a laparoscopic biopsy before treatment. The exclusion criteria for the study were (1) patients referred to other hospitals after diagnosis, (2) resectable but non-operated cases and (3) unresectable cases without any chemotherapy or radiotherapy.

The following clinical data were collected: patient demographics, laboratory findings including carbohydrate antigen 19-9, radiologic and pathologic features, operative data, adjuvant or palliative chemotherapy or radiation therapy and follow-up data. The tumour diameter was defined as the maximal diameter of the tumour measured from the gross lesion (surgical cases) or radiologic images (unresectable cases). Resection margin involvement was defined as tumours cells in the margin or within 1 mm of the margin. None of our patients received neoadjuvant chemotherapy or radiation therapy. The institutional review board approved this study (KC18RESI0048).

2.2. Treatment strategy

All patient assessment and treatment decisions were made at a meeting of the Catholic University Pancreatic Cancer Group of Seoul St. Mary's Hospital, which was composed of expert gastroenterologists, oncologists, surgeons, radiologists and pathologists. If a case was determined with resectable or borderline resectable disease in the meeting, upfront surgery combined with active lymphadenectomy was performed. To reduce the