Available online at www.sciencedirect.com

ScienceDirect

EJSO 43 (2017) 1711–1717

EJSO the Journal of Cancer Surgery

www.ejso.com

Retrospective cohort analysis of neoadjuvant treatment and survival in resectable and borderline resectable pancreatic ductal adenocarcinoma in a high volume referral centre

M. Itchins [a,c,*], J. Arena [a], C.B. Nahm [b,c], J. Rabindran [b,c], S. Kim [b], E. Gibbs [d], S. Bergamin [a], T.C. Chua [b], A.J. Gill [c,e], R. Maher [f], C. Diakos [a,c,g], M. Wong [h], A. Mittal [b,c], G. Hruby [a,c], A. Kneebone [a,c], N. Pavlakis [a,c,g], J. Samra [b,c], S. Clarke [a,c,g]

[a] *Department of Oncology, Royal North Shore Hospital, Sydney, NSW, Australia*
[b] *Upper GI Surgical Unit, Department of Gastrointestinal Surgery, Royal North Shore Hospital, Sydney, NSW, Australia*
[c] *Sydney Medical School (Northern), The University of Sydney, Australia*
[d] *National Health and Medical Research Council Clinical Trial Centre (NHMRC CTC), The University of Sydney, Australia*
[e] *Cancer Diagnosis and Pathology, Kolling Institute, Royal North Shore Hospital, Sydney, Australia*
[f] *Department of Radiology, Royal North Shore Hospital, Australia*
[g] *Northern Cancer Institute, Sydney, NSW, Australia*
[h] *Department of Medical Oncology, Gosford Hospital, New South Wales, Australia*

Accepted 9 June 2017
Available online 28 June 2017

Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is a deadly disease. Neoadjuvant therapy (NA) with chemotherapy (NAC) and radiotherapy (RT) prior to surgery provides promise. In the absence of prospective data, well annotated clinical data from high-volume units may provide pilot data for randomised trials.

Methods: Medical records from a tertiary hospital in Sydney, Australia, were analysed to identify all patients with resectable or borderline resectable PDAC. Data regarding treatment, toxicity and survival were collected.

Results: Between January 1 2010 and April 1 2016, 220 sequential patients were treated: 87 with NA and 133 with upfront operation (UO). Forty-three NA patients (52%) and 5 UO patients (4%) were borderline resectable at diagnosis. Twenty-four borderline patients received NA RT, 22 sequential to NAC. The median overall survival (OS) in the NA group was 25.9 months (mo); 95% CI (21.1–43.0 mo) compared to 26.9 mo (19.7, 32.7) in the UO; HR 0.89; log-ranked p-value = 0.58. Sixty-nine NA patients (79%) were resected, mOS was 29.2 mo (22.27, not reached (NR)). Twenty-two NA (31%) versus 22 UO (17%) were node negative at operation (N0). In those managed with NAC/RT the mOS was 29.0 mo (17.3, NR). There were no post-operative deaths with NA within 90-days and three in the UO arm.

Discussion: This is a hypothesis generating retrospective review of a selected real-world population in a high-throughput unit. Treatment with NA was well tolerated. The long observed survival in this group may be explained by lymph node sterilisation by NA, and the achievement of R0 resection in a greater proportion of patients.

Keywords: Pancreas; Adenocarcinoma; Neoadjuvant; Borderline; Resectable; Operative

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fifth most common cause of cancer death in developed regions,[1]

* Corresponding author. Northern Cancer Institute, 38 Pacific Highway St Leonards, New South Wales, 2065, Australia. Fax: +61 294631092.
E-mail address: mitchins@gmail.com (M. Itchins).

http://dx.doi.org/10.1016/j.ejso.2017.06.012

with a median survival of 6 months and 20% 5-year overall survival (OS) in resected patients.[2] Unfortunately, over 80% of patients present with unresectable disease and is thus a systemic disease from the time of diagnosis.[3]

Recent evidence indicates that in operative cases, completion of multimodality therapy is associated with improved oncologic outcomes.[4] Such therapy can be difficult to deliver after upfront surgery.[5] Neoadjuvant (NA) chemotherapy (NAC) and/or radiation therapy (RT) may provide a survival benefit through the following mechanisms: (i) early treatment of micro-metastatic disease, (ii) improved selection of patients with biologically favourable disease, (iii) tumour down-staging enabling better surgical outcomes, and (iv) in providing a "window of opportunity" for assessment of novel therapeutics.[5–9]

Perceived detriments of NA include: (i) potential progression of disease and missed "window of opportunity" for resection, (ii) toxicity from NA treatment precluding definitive surgical resection, and (iii) the need for histopathological confirmation of PDAC, which may be more difficult to obtain without surgery.[7]

A universal consensus classification on the definition of "borderline resectable" disease does not exist. It implies a greater chance of incomplete resection with upfront surgery.[9–12] Additional patients are classified based on clinical factors independent of anatomy, such as age and comorbidities.[11]

Surgical resection offers greatest potential for long-term survival and cure.

Randomised data to support NA therapy are currently lacking, with some trials ongoing and data to date showing heterogeneity. Multiple single-institution phase I–II studies have demonstrated that patients undergoing neoadjuvant systemic therapy are more likely to complete it, have clear surgical resection margins (R0) and node negative disease. These reports, including those with RT, demonstrated longer survival.[4,11,13–18] Many studies used therapies that are now outdated.[19–22] Collectively, these data suggest that NA therapy may enhance resectability and reduce local recurrence without worsening toxicity.[23,24]

In patients who received NA therapy, additional post-operative chemotherapy has demonstrated improved survival compared with adjuvant therapy alone.[25]

Although recent combination chemotherapy schedules in the advanced disease setting have improved survival outcomes, evidence for their use in early disease is lacking, and various regimens are used in practice.[26–28]

We report our local experience with NAC and/or NA RT in resectable and borderline resectable PDAC, compared with those managed with upfront operation (UO).

Patients

Approval for the conduct of this study was obtained from the Northern Sydney Local Health District Human Research Ethics Committee.

A retrospective cohort analysis of all patients who received NA therapy and UO and adjuvant therapy for PDAC across two campus hospitals in Northern Sydney, Australia was performed.

Patients were identified by searching electronic medical records. All patients were discussed in a multidisciplinary meeting (MDT) and deemed appropriate for NA therapy by pancreas cancer specialists.

Patients underwent preoperative evaluation including clinical history, physical examination, complete laboratory assessment and preoperative imaging with triple-phase CT scans. Histopathological/cytological confirmation of PDAC and normal laparoscopy were required. Abdominal MRI and/or PET scans were performed as required by the MDT.

Methods

Neoadjuvant treatment selection

Patients were considered for NA therapy if there was: any degree of local vessel involvement on imaging (stage 1b–3); if they were enrolled on a clinical trial evaluating NA therapy without vessel involvement[29]; based on patient factors such as age, comorbidities or preference. Only borderline resectable patients were deemed appropriate for NA RT.

Local Australasian anatomical staging guidelines were utilised.[30] Local and clearly resectable stage 1a/1b tumours were considered for NA if enrolling in a prospective clinical trial or if venous involvement >90. Borderline tumours, i e. stage 2a/2b, were all considered for NA therapy. Locally advanced stage 3 patients were included if deemed appropriate for NA. Patients regarded borderline resectable based on clinical factors were considered for NA to elucidate their ability to tolerate treatment and the biology of the tumour.[30]

All patients received 6 months of perioperative chemotherapy and if deemed appropriate, 25–30 fractions of NA RT with radio-sensitising fluorouracil based chemotherapy after completion of 'induction' NAC. Chemotherapy regimen was at the discretion of the treating physician based on patient assessment of tolerability.

Two surgeons performed all operations (JS, AM).

Data were collected on baseline patient characteristics, imaging, treatment received and surgical status. The pathological characteristics were assessed using a standardized structured surgical pathology report[31] and an R0 margin was defined as being >1 mm clear of tumour (R0 > 1 mm).[32] Toxicity data were collected for all procedures-length of hospital stay and post-operative mortality.

Histology, surgery, recurrence and death were recorded.

Statistical analyses

Time to death and relapse were calculated using the time between the date of diagnosis and the date of death or last known contact. Survival data were presented using the