

## **Pancreatic Cancer: The Effect of Specialization and New Medical Treatment**

**Generoso Uomo, Raffaele Pezzilli**

Internal Medicine Department, 3rd Division, A. Cardarelli Hospital. Naples, Italy.  
Department of Internal Medicine, Sant'Orsola-Malpighi Hospital. Bologna, Italy

Within the past decade, many studies of patients having pancreatic cancer have shown a reduced post-operative morbidity and mortality rate as well as longer survival when treated in specialist regional Centres. A significant reduction in post-operative mortality rates in high- versus low-volume hospitals was observed both in the USA [1] and in Europe [2]. In-hospital mortality rates range from 14 to 28% in Centres with 1 to 5 major pancreatic resections per year whereas a percentage ranging from 2 to 6% is reported in Centres treating more than 15 patients per year. The effect of pancreatic cancer resection volume on postoperative mortality has no threshold value but is continuous [3]. The effect seen on reduced mortality by increased volume is related to institution rather than to any individual surgeon and it is called *working-team* effect [4]. In addition, the volume-mortality effect is associated with a higher resectability rate which very often was more than 15% in comparison with the 2-4% observed in low-volume Centres [5,6]. Finally, the volume-mortality effect is associated with higher long-term survival: 25% in low-volume Centres and 37% in high-volume ones [7]. Recently, an interesting study on this issue comes from Scotland [8]. The aim of this study was to ascertain if there was any evidence of benefit for the specialized care of patients with pancreatic cancer in Scotland. The records of patients diagnosed with pancreatic cancer during the

period 1993-1997 were identified. Three indicators of co-morbidity were calculated for each patient. The operative procedures were classified as resection, other surgery or biliary stent. Prior to analysis, consultants were assigned as specialist pancreatic surgeons, clinicians with an interest in pancreatic disease or non-specialists. Data were analyzed with regard to 30-day mortality rates and survival outcome. The final study population included 2,794 patients. The 30-day mortality rate following resection was 8%, and hospital or consultant volume did not affect postoperative mortality. The 30-day mortality rate following palliative surgical operations was 20%, and consultants with higher case loads or with a specialist pancreatic practice had significantly fewer postoperative deaths ( $P=0.014$  and  $0.002$ , respectively). For patients undergoing potentially curative or palliative surgery, the risk of death was higher in patients having advanced years of age, increased co-morbidity or metastatic disease, and was significantly lower for those managed by a specialist or by a clinician with an interest in pancreatic disease. The risk of death 3 years after the diagnosis of pancreatic cancer is higher among patients undergoing surgical intervention by non-specialists. This study confirms previous experiences in this field and substantiates the policy adopted in Great Britain where the National Health Service stated that "*surgery for pancreatic cancer should be carried out only by*

*specialist Pancreatic Cancer Teams in designated large cancer Centres, which will serve and adult population of 2-4 million” and that “all surgically fit patients with potentially respectable disease should proceed to surgical exploration in a Regional Centre” [3].*

Regarding the medical treatment of pancreatic cancer, in recent years many studies have been published with the aim of defining the best chemotherapeutic regimens for patients with advanced pancreatic cancer. In this respect, many attempts with gemcitabine-based combination schedules have been proposed. The study from the Anderson Cancer Center of Houston, TX, [9] was focused on assessing the classical parameters of in-vivo chemosensitivity (response rate, time to disease progression, survival duration and rate, and toxicity) of the combination of cetuximab and gemcitabine in patients with epidermal growth factor receptor (EGFR)-expressing advanced pancreatic cancer. Patients with measurable locally advanced or metastatic pancreatic cancer who had never received chemotherapy for their advanced disease and had immunohistochemical evidence of EGFR expression were eligible for this multicenter phase II trial. Patients were treated with cetuximab at an initial dose of 400 mg/m<sup>2</sup>, followed by 250 mg/m<sup>2</sup> weekly for 7 weeks. Gemcitabine was administered at 1,000 mg/m<sup>2</sup> for 7 weeks, followed by 1 week of rest. In subsequent cycles, cetuximab was administered weekly, and gemcitabine was administered weekly for 3 weeks every 4 weeks. The results of the study were as follows: a) sixty-one patients were screened for EGFR expression, 58 patients (95%) had at least 1 positive staining and 41 were enrolled in the trial; b) five patients (12.2%) achieved a partial response, and 26 (63.4%) had stable disease; c) the median time to disease progression was 3.8 months, and the median overall survival duration was 7.1 months, d) one-year progression-free survival and overall survival rates were 12% and 31.7%, respectively; e) the most frequently reported grade 3 or 4 adverse events were neutropenia (39.0%),

asthenia (22.0%), abdominal pain (22.0%), and thrombocytopenia (17.1%). In conclusion the proposed regimen, cetuximab associated with gemcitabine, seems to be promising when used against advanced pancreatic cancer, at least as a tumor growth control rate. However, further clinical investigation is warranted.

Recent developments in balloon catheter methodology have made hypoxic abdominal perfusion with anti-tumor agents possible with only minimal invasive surgery. A double cytotoxic effect induced by the hypoxia and the chemotherapeutic agent was obtained with good results observed especially for liver cancer. The initial reports on this modality and celiac axis stop-flow infusion for treatment of pancreatic cancer were very promising in terms of tumor response, median survival and pain reduction, but recent reports, however, have not been able to confirm these results and some have disputed the efficacy of these currently still used treatment modalities. Physicians from the Oncology Department of the Erasmus Medical Center in Rotterdam [10] have performed a phase II trial of hypoxic abdominal perfusion associated with chemotherapy (melphalan plus mitomycin C) in which 21 patients with advanced pancreatic carcinoma were included. The schedule consisted of hypoxic abdominal perfusion with mitomycin C and melphalan followed by celiac axis infusion with the same agents six weeks later. Tumor response was assessed by abdominal-CT scan and by determining tumor markers. The effect on pain reduction was assessed by evaluation of pain registration forms. As expected, hypoxic abdominal perfusion resulted in augmented regional drug concentrations. One patient died after celiac axis infusion due to acute mesenteric ischaemia. One agent-toxicity related death was observed in the phase-I study. Significant hematological toxicity was observed after hypoxic abdominal perfusion and celiac axis infusion at maximum tolerable doses. No patients were considered resectable after treatment. Median survival after hypoxic abdominal perfusion was 6 months (range 1-29). Pain reduction was experienced by only

5/18 patients and was short-lived. The conclusions of the study were negative as hypoxic abdominal perfusion and celiac axis infusion with mitomycin C, and melphalan did not demonstrate any benefit in terms of tumor response, median survival and pain reduction, compared to less invasive treatment options. In addition, this treatment was associated with significant toxic side-effects and even one procedure related death. Palliative regimens able to improve or stabilize the quality of life still remain the best option for patients with advanced and metastatic pancreatic cancer.

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**Keywords** Drug Therapy; Infusions, Parenteral; Morbidity; Mortality; Pancreatic Neoplasms; Postoperative Complications

#### Correspondence

Generoso Uomo  
Internal Medicine Department  
3<sup>rd</sup> Division  
A. Cardarelli Hospital  
Via Cardarelli, 9  
80131 Napoli  
Italy  
Phone: +39-081.747.2101  
Fax: +39-081.747.4042  
E-mail: [generoso.uomo@ospedalecardarelli.it](mailto:generoso.uomo@ospedalecardarelli.it)

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