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IORT of pancreatic cancer

Intra-operative radiotherapy (IORT) in pancreatic cancer: Joint analysis of the ISIORT-Europe experience

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ABSTRACT

Purpose: A joint analysis of data from five contributing centers within the ISIORT-Europe program was performed to investigate the main contributions of intra-operative radiotherapy (IORT) to the multidisciplinary treatment of pancreatic cancer.
Materials and methods: Patients with a histologic diagnosis of carcinoma of the pancreas, with an absence of distant metastases, undergoing surgery with radical intent and IORT were considered eligible for participation in this study.
Results: From 1985 to 2006, a total of 270 patients were enrolled in the study from five European Institutions. Surgery was performed in 91.5% of cases and complicated by adverse events in 59 cases. External radiotherapy (ERT) preceded surgery in 23.9% of cases. One-hundred and six patients received further ERT. After surgery + IORT, median follow-up was 96 months (range 3–180). Median local control was 15 months, 5-year local control was 23.3%. Median overall survival was 19 months, while 5-year survival was 17.7%. A significantly greater local control and survival were observed in patients undergoing preoperative radiotherapy (LC: median not reached; OS: median 30 months) compared to patients treated with postoperative ERT alone (LC: median 28 months; OS: median 22 months), and to patients submitted to IORT exclusively (LC: median 8 months; OS: median 13 months) ($p < 0.0001$).
Conclusion: From this joint analysis emerges the fact that preoperative radiotherapy increases the effects of IORT in terms of local control and overall survival. The 5-year local control of 23.3% confirms the beneficial "sterilizing" effect of IORT on the tumor bed.
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Despite the important improvements made in the fields of surgery, chemotherapy and radiation therapy, pancreatic cancer remains one of the most lethal malignancies with an overall survival of less than 5% at 5 years [1]. Most tumors of the pancreas are indeed diagnosed when the disease is in a locally advanced stage and is not likely to undergo surgical resection. Among patients with apparently resectable disease who are going to surgical exploration, only 20–40% of cases are effectively operable, and even in cases where a radical resection with negative margins is obtained, 5-year survival does not exceed 30%, with half the survived patients going to have a recurrence over the next 5 years [2]. Moreover, the high rate of local recurrence after surgery is probably due to the frequent presence of residual microscopic disease, which generally requires higher doses of external beam radiotherapy (ERT), up to 60 Gy with standard fractionation [3]. On the other hand, the immediate proximity to critical structures (bone marrow, spinal cord, kidneys, liver, and intestine) limits the dose of radiation that can be administered to the tumor bed with conventional ERT. The intra-operative radiotherapy (IORT) appears to be an ideal therapeutic strategy for this disease, having

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the advantage of enabling the delivery of high doses of radiation to areas that are at risk for microscopic disease, saving critical organs and reducing the possibility of inducing radiotoxicity. This technique allows a theoretical increase in the radiation therapeutic index to tumor compared to the adjacent organs at risk (OAR), for at least three reasons:

- The biological effectiveness of a single, high dose of radiation is greater than the same dose administered in a fractionated regimen.
- The radiation is directed exactly on the area with an increased risk of tumor relapse (or persistence).
- Irradiation of the dose-limiting OAR, such as choledocus, small intestine, stomach or bone marrow, can be spared from radiation during surgery through the manual mobilization of healthy tissues from the treatment volume, through the use of appropriate lead protections or through the proper use of an electron beam with energies sufficient to limit the radiation on deep structures [4].

Since 1985, five European institutions (Istituto San Raffaele, Milan, Heidelberg Universität, Catholic University of the Sacred Heart, Rome, Hospital Universitario G. Marañon, Madrid, Paracelsus Universität, Salzburg,) have treated a total of 270 pancreatic cancer patients with surgery + IORT, associated or not to ERT. In this study, a joint analysis of their experience was gathered within the International Society of Intra-operative Radiotherapy (ISIORT) – Europe program, in order to investigate, on a wide sample of patients, evidence of the contribution of IORT to the multidisciplinary treatment of pancreatic cancer.

Patients and methods

Inclusion criteria

Patients with a histologically confirmed diagnosis (obtained by biopsy or surgical resection) of pancreatic adenocarcinoma, with the absence of distant metastases, undergoing surgery with radical intent and IORT were considered eligible for this study. Further inclusion criteria were: age >18 years, performance status <2 [5], life expectancy exceeding 12 weeks, white blood cells count $\geqslant 3{,}5 \times 10^{9}\,L^{-1}$; platelet count $\geqslant 150 \times 10^{9-1}$ and written informed consent to surgery with IORT. Pre-treatment evaluation consisted of general examination, abdominal magnetic resonance imaging (MRI) or CT-scan. ERCP was performed when indicated. Patients were ineligible in the presence of clinical history of previous malignancy or presence of distant metastasis at the staging work-up.

Study design

The aim of this joint analysis is to investigate in a large series of pancreatic cancer patients submitted to surgery with radical intent whether IORT can ameliorate the prognosis by improving local control and/or survival. After the clinical staging work-up being performed by thorax–abdomen CT-scan, and/or ERCP, the patients underwent neoadjuvant radiotherapy if they were in a situation of locally advanced disease, not allowing, according to the local surgeon, a surgical approach and, after clinical restaging, submitted to surgery with radical intent and IORT if feasible. An adjuvant radiotherapy was permitted at the discretion of the study investigators in each individual center. All schemes of radiotherapy were accepted, and each center was required to follow-up the enrolled patients after the end of study treatment as follows: quarterly during the first 3 years, half-yearly during the 4th and 5th year, and yearly afterwards.

Treatment toxicity recorded during the years was evenly converted at the moment of the analysis, according to the criteria of the Radiation Therapy Oncology Group [6], whereas the following surgical complications were also considered: death, bleeding (more than 500 cc), re-laparotomy, abdominal abscess, pancreatic fistula and sepsis, in a period of 30 days following surgery + IORT.

Statistical analysis

Local control (LC), defined as the absence of recurrence in the primary site of disease, and overall survival (OS) were calculated by the Kaplan–Meier actuarial method [7], starting from surgery + IORT until the date of local recurrence or death, respectively, or up to the date of last follow-up. Recurrence in the primary site of disease, documented by CT-scan, was considered an event for local control, whereas death from pancreatic cancer was considered an event for overall survival. Differences between the survival curves of the subsets of patients were analyzed using the log-rank test method [8]. Cox' logistics regression was used to perform the multivariate analysis and to calculate the hazard ratio [9].

Statistical analysis was performed using the program SYSTAT, Version 11 for Microsoft Windows.

Results

From 1985 to 2006, a total of 270 patients were enrolled in the study from the five above-mentioned institutions. The number of patients enrolled for each center is shown in Table 1.

The patient median age was 61.5 years and the other characteristics are described in Table 2.

In Table 2, it is also shown that most of the patients enrolled had a locally advanced disease (the patient's staging data were upgraded, at the moment of the analysis, to the sixth edition of the TNM, AJCC 2002), with tumor extending beyond the pancreas in 86.6% of cases. One hundred and seventy-six patients (67.4%) had also histologically confirmed lymph node metastases, while 12 patients had liver metastases not identified during the staging procedures.

Surgery was performed in 247 cases (91.5%), with absent residual tumor (R0) in 53.4% of cases, microscopical residual disease (R1) in 27.4% and macroscopical residual disease (R2) in 19.2% of cases. Surgery was preceded by ERT in 63 (23.9%) cases, and complicated by adverse events in 59/247 cases (Table 3). Overall, only 4/247 patients died as a result of surgical complications.

After surgery + IORT, 106 patients (40.1%) received further ERT. A total of 32 patients (11.8%) received concomitant chemoradiation before ($n = 24/63$) or after ($n = 8/106$) surgery + IORT.

ERT was delivered to pancreas/tumor bed and regional lymph nodal stations with a multiple fields technique according to the single Institution policy. A median dose of 45 Gy was administered (range 18–61). IORT was delivered by electrons of 6–12 MeV, with a median dose of 15 Gy (range 7.5–25).

Acute toxicity related to radiation treatment was slight, and no case exceeded grade 2.

Table 1
Patients enrolled by single institution

Institution	No. patients	%
Milan, Istituto San Raffaele	117	43.3
Heidelberg Universität	85	31.5
Rome, Policlinico Gemelli	26	9.6
Madrid, Hospital Universitario G. Marañon	23	8.5
Salzburg, Paracelsus Universität	19	7.1
Total	270	100