



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. Marañón, 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 (ISIRT) – 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 $\geq 3.5 \times 10^9 \text{ L}^{-1}$; platelet count $\geq 150 \times 10^9 \text{ L}^{-1}$ 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. Marañón	23	8.5
Salzburg, Paracelsus Universität	19	7.1
Total	270	100

Table 2
Patient's characteristics

Characteristics	No.	%
Median age (range)	61.5 (25–74)	
Stage ^a		
pT1	11	4.2
pT2	24	9.2
pT3	150	57.7
pT4	75	28.9
pN0	85	32.6
pN1	176	67.4
pM1 (liver) ^b	12	4.5
Surgery		
Explorative laparotomy	23	8.5
Radical surgery	247	91.5
Surgical margins ^a		
R0	144	53.4
R1	74	27.4
R2	52	19.2
Radiotherapy ^a		
Pre-operative ERT + IORT	63	23.9
IORT + ERT post-operative	106	40.1
Exclusive IORT	95	36.0
Radiotherapy doses		
ERT median dose (range)	45 (1.8–61)	
IORT median dose (range)	15 (7.5–25)	

^a Data not available for the totality of patients.

^b cM0 at the staging work-up.

Table 3
Surgical adverse events

Event	% ^a
Pancreatic fistula	27
Delayed gastric emptying	21.6
Emorrhage	18.4
Re-laparotomy	15.3
Abdominal abscess	13.9
Sepsis	3.1
Peri-operative mortality	2.2

^a Data available for 174 patients.

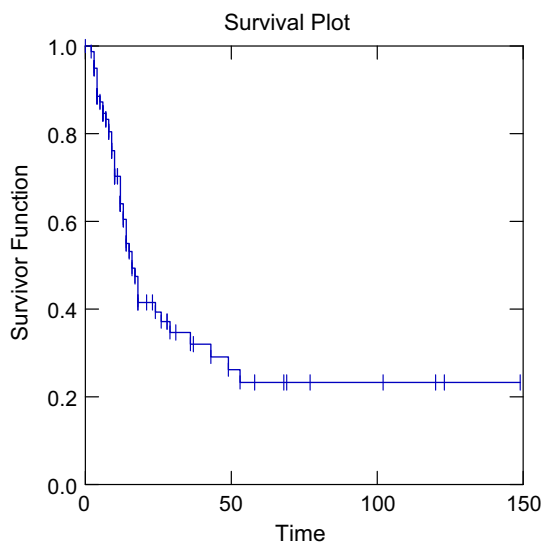


Fig. 1. Local control.

Median follow-up was 96 months (range 3–180). Median LC was 15 months, whereas 5-year LC was 23.3% (Fig. 1). LC was significantly associated with tumor size (median not reached for T1–2, 13 months for T3–4, $p < 0.0001$), residual tumor (median 17 months for R0–1, 6 months for R2, $p < 0.0001$), and positive lymph nodal status (median 53 months for N0, 12 months for N1, $p < 0.0001$) (Fig. 2). A significantly greater LC was observed in patients undergoing preoperative radiotherapy (median LC not reached) compared to patients treated with postoperative ERT (median LC 28 months), and to patients submitted to IORT exclusively (median LC 8 months) ($p < 0.0001$, Fig. 3). The Cox' logistic regression revealed that tumor size, lymph node positivity and timing of external radiotherapy significantly affect local control with a hazard ratio (HR) of 1.8 (95% CI 1.06–3.2, $p = 0.03$), 2.6 (95% CI 1.2–5.6, $p = 0.0009$) and 3.3 (95% CI 1.8–6.2, $p < 0.0001$), respectively.

Median OS was 19 months, while 5-year OS was 17.7% (Fig. 4). The univariate analysis revealed that neither tumor size, residual tumor after surgery, nor the lymph nodal status was significantly related to survival. In particular, median survival was 16 months for patients with stage T1–2 and 19 months

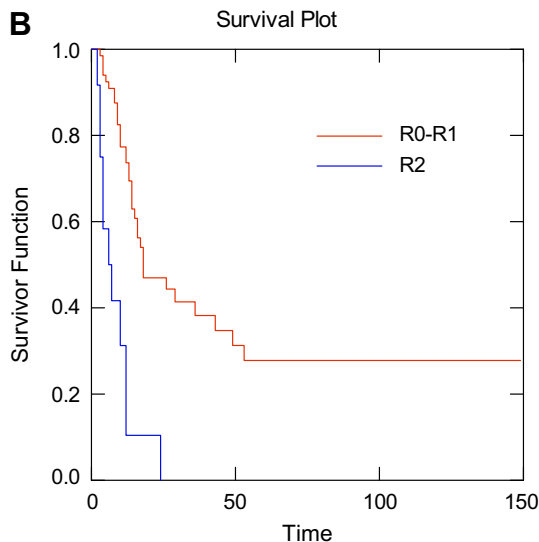
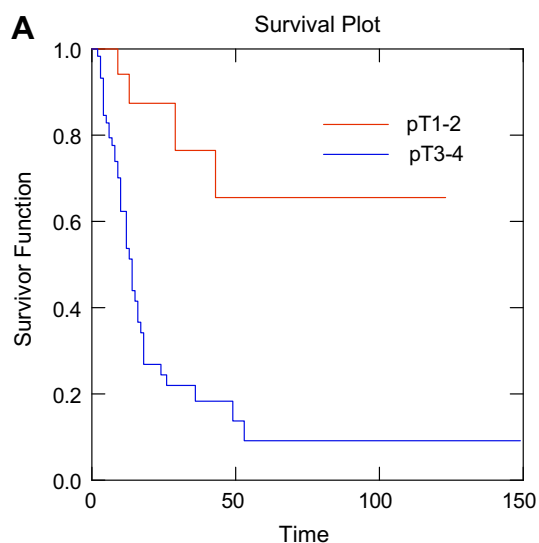


Fig. 2. Local control stratified by T (A) and residual tumor (B).

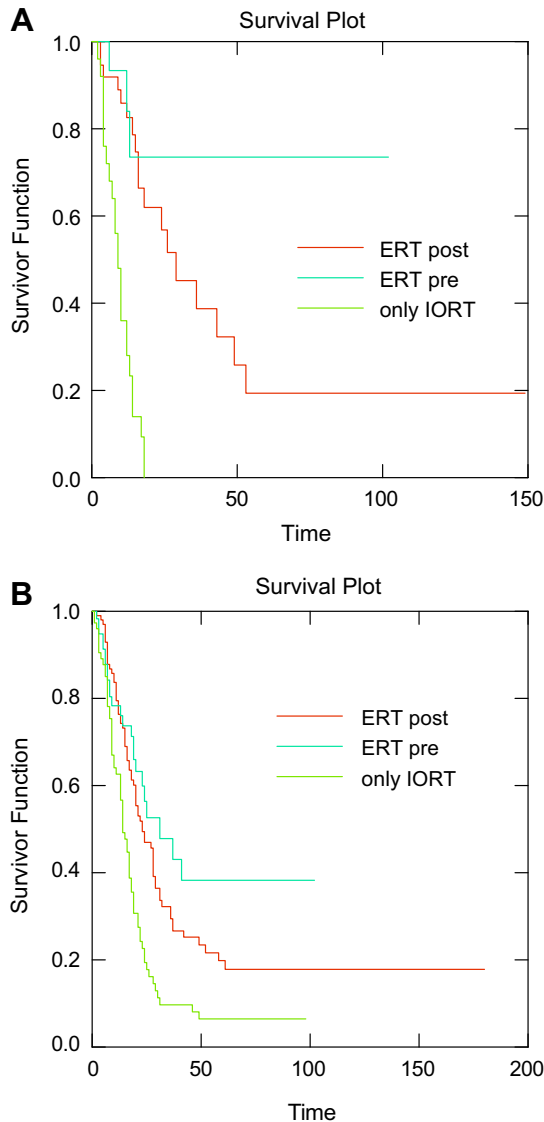


Fig. 3. (A) Local control stratified by timing of ERT. (B) Overall survival stratified by ERT timing.

for T3–4 cases ($p = 0.32$), and 19 months for patients with absent/microscopic residual tumor versus 18 months for patients with macroscopic residual disease ($p = 0.31$). Median OS was 18 and 19 months, respectively, for N0 and N1 cases. Only the timing of ERT was observed to affect survival, since a significantly longer OS was registered in patients undergoing preoperative ERT (median OS 30 months) compared to patients treated with postoperative ERT (median OS 22 months), or to patients submitted to IORT exclusively (median OS 13 months) ($p < 0.0001$, Fig. 3). The Cox' logistic regression revealed that lymph nodal status and the timing of external radiotherapy significantly affect survival, with a hazard ratio (HR), respectively, of 1.6 (95% CI 1.1–2.3, $p = 0.008$) and 1.4 (95% CI 1.1–1.8, $p = 0.008$). As shown in Fig. 5, interestingly a prolonged survival was observed within the subset of patients who remained recurrence-free for more than 2 years: in fact in this group, the 3- and 5-year OS was of 31.9% and 28.4%, respectively, compared to 11.9% and 0% for patients who had a local recurrence within the first 2 years after IORT ($p = 0.04$).

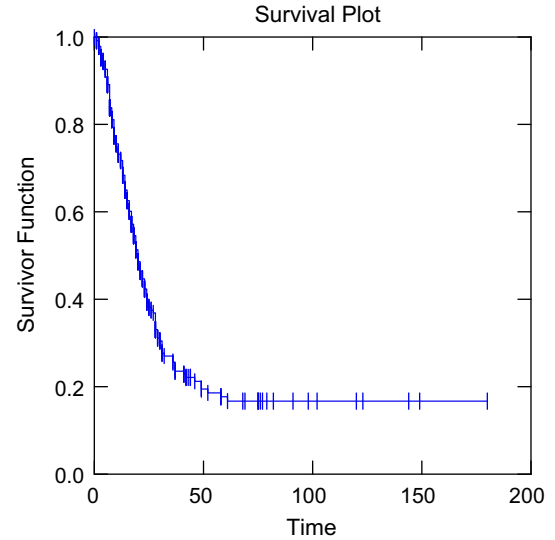


Fig. 4. Overall survival.

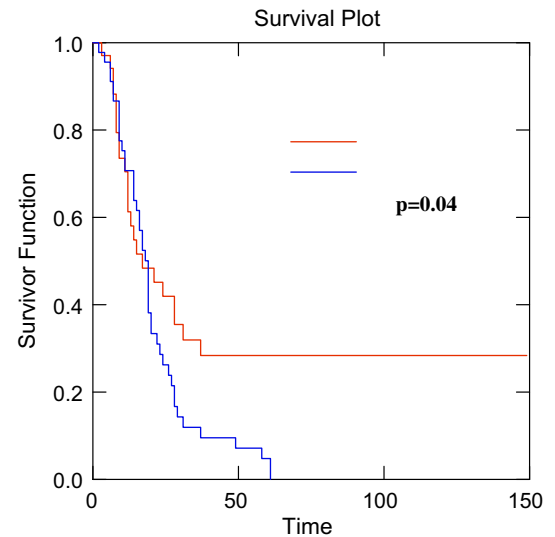


Fig. 5. Overall survival stratified on the basis of the freedom from local recurrence < 2 years (blue line) or > 2 years (red line).

Discussion

With a mortality/incidence ratio of approximately 0.9, carcinoma of the pancreas is still one of the most hardly curable malignancies, especially taking into account that despite the progress made in terms of surgery, chemotherapy and radiation therapy, the overall 5 year-survival of this disease did not significantly improve in the last 25 years [1]. A complete resection of the tumor remains the main chance of cure for patients suffering from this disease, but radical surgery is actually achievable in less than 20% of cases [10], so integrated therapies represent an important strategy to improve the prognosis of this disease [11].

Since its first experimental experiences, IORT has been considered an interesting approach for the treatment of pancreatic cancer. This technique, in fact, allows the delivery of higher doses of radiation than conventional methods, thus providing, at least in theory, a better local control. Because of the complexity related to surgical pancreatic resection, the first IORT investigators expressed concern about a possible increase in toxicity when IORT

was combined with pancreatectomy. However, the feasibility of the technique was demonstrated as early as 1983 at the National Cancer Institute (NCI), where a patient with locally advanced cancer survived disease-free for more than 19 months after total pancreatectomy with portal resection and IORT on the tumor bed and regional lymph nodes [12]. Afterwards, the NCI reported the experience on further 24 patients randomized to receive IORT (20 Gy) or observation (stage I) or ERT (50 Gy, stages II–IV). Excluding 7 peri-operative deaths, an improvement of local control ($p = 0.06$) and median overall survival in the IORT group (18 vs. 12 months, $p = 0.01$) was registered, but no difference in terms of disease-free survival was observed [13].

Over the last decades the experimental, technical and clinical applications of IORT have undergone substantial progress: most of the experimental studies in this direction have been conducted by the National Cancer Institute and the University of Colorado, which produced important data especially regarding short- and long-term tolerance of normal tissues frequently irradiated with IORT [14–21].

Several studies, published over the past 30 years, described the favorable effects of IORT in pancreatic cancer [12,13,22–24], but are limited with regard to any clear interpretation. Reports in the literature on IORT in pancreatic cancer indicate that this therapeutic technique has been used in the context of multiple treatment strategies: with or without radical surgery [25,26], as the only radiotherapeutic part of treatment, with or without chemotherapy and/or radiotherapy induction [25,27]. Furthermore, the majority of the reported experiences were performed in a single Institution, outside randomized controlled studies, and involved limited number of patients, thus contributing to an increase of evidence, but without offering a clear message on the real role of IORT in the clinical approach to pancreatic cancer.

This joint analysis examined the broadest series ever collected on IORT in pancreatic cancer treatment. The surgical complications rate is similar to that reported in the literature for conventional surgery [28]. Median LC of 15 months and median OS of 19 months favourably compare with the data concerning other treatment strategies on this disease [29], as do the results regarding 5-year LC (23.3%) and 5-year OS (17.7%).

A trend seems to emerge from this study, that external radiotherapy may increase the effects of IORT in terms of local control and overall survival, since longer LC and OS were observed in patients submitted to ERT + IORT. These findings, however, may be explained by a selection bias precluding surgery + IORT to patients progressing during preoperative ERT, as well as excluding further ERT patients in progression after IORT. However, the significantly greater LC and OS observed in patients undergoing preoperative radiotherapy (LC: median not reached; OS: median 30 months) compared to that of patients treated with postoperative ERT (LC: median 28 months; OS: median 22 months), and to patients submitted exclusively IORT (LC: median 8 months; OS: median 13 months) ($p < 0.0001$), suggest that a preoperative treatment may act as a filter selecting patients who are already affected by occult metastatic disease at the moment of enrolment into the study and destined to progress during the time of induction therapy, sparing them of surgery and IORT. Similar results were already reported by Pisters et al. [30] who obtained high survival rates in patients treated with preoperative chemoradiation followed by radical surgery and IORT at the MD Anderson Cancer Center. More recently, this theory of the “filter-induction” has been explored on a wide retrospective study by Huguet et al. [31], who demonstrated a significant improvement in survival for patients submitted to chemoradiation after a period of induction chemotherapy.

An interestingly prolonged survival was observed in our analysis, within the subset of patients who remained recurrence-free for more than 2 years: in fact, in this group, the 3- and 5-year overall

survival was of 31.9% and 28.4%, respectively, compared to 11.9% and 0% for patients who had a local recurrence within the first two years from IORT. These data support the idea that, while metastasis still remains the main challenge for this disease, the improvement of local control by higher radiotherapy doses may have an impact on the survival of patients with lower trend to disease spread. It is therefore possible to conclude that IORT preceded by ERT seems to have a positive impact on local control even if a more efficient strategy in the multimodality treatment is needed to control micrometastases and to select patients who could benefit by surgery and local therapies.

Unfortunately in this study, which began in the mid 1980s, the use of concurrent chemotherapy with radiation therapy was optional, but recent evidence in the literature has proved that chemoradiation is more effective than radiotherapy alone in determining resectability of locally advanced tumors [32,33], and that new drugs such as gemcitabine [34,35], taxanes [36], platinum compounds [37], may contribute to further improve the prognosis of this disease, being not only good antiproliferative drugs, but also potent radiosensitizing agents. In this new scenario, after an induction chemoradiation which may help identify patients who cannot benefit from a local treatment because they are affected early by systemic disease, in those cases where radicality is obtained with surgery, IORT could play an important role in warranting a prolonged control of this disease.

References

- [1] Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. *CA Cancer J Clin* 2007;57:43–66.
- [2] Brennan MF. Adjuvant therapy following resection for pancreatic adenocarcinoma. *Surg Oncol Clin N Am* 2004;13:555–61.
- [3] Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas – 616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg* 2000;4:567–79.
- [4] Kinsella TJ, Sindelar WF. Intraoperative radiotherapy for pancreatic carcinoma. Experimental and clinical studies. *Cancer* 1996;78:598–604.
- [5] Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5: 649–55.
- [6] Radiation Therapy Oncology Group. Cooperative Group common toxicity criteria v 2.0 1999. Available from: www.rtog.org/members/toxicity/tox.html.
- [7] Kaplan FL, Meier P. Non parametric estimation from incomplete observations. *Am J Stat Assoc* 1958;53:457–81.
- [8] Peto R, Peto J. Asymptotically efficient rank invariant procedures. *J R Stat Soc* 1972;135:185–207.
- [9] Cox DR. Regression model and life tables. *J R Stat Soc* 1972;34:187–220.
- [10] Alexakis N, Halloran C, Rarati M, et al. Current standards of surgery for pancreatic cancer. *Br J Cancer* 2004;91:1410–27.
- [11] Russo S, Butler B, Ove R, Blackstock AW. Locally advanced pancreatic cancer: a review. *Semin Oncol* 2007;34:327–33.
- [12] Sindelar WF, Kinsella TJ, Pepper J, et al. Experimental and clinical studies with intraoperative radiotherapy. *Surg Gynecol Obstet* 1983;157:205–19.
- [13] Sindelar WF, Hoekstra H, Restrepo C, Kinsella TJ. Pathological tissue changes following intraoperative radiotherapy. *Am J Clin Oncol* 1986;9:504–9.
- [14] Kinsella TJ, Sindelar WF, DeLuca AM, et al. Tolerance of the canine bladder to intraoperative radiation therapy: An experimental study. *Int J Radiat Oncol Biol Phys* 1988;14:939–46.
- [15] Kinsella TJ, DeLuca AM, Barnes M, et al. Threshold dose for peripheral neuropathy following intraoperative radiotherapy (IORT) in a large animal model. *Int J Radiat Oncol Biol Phys* 1991;20:697–701.
- [16] Sindelar WF, Pepper J, Travis EL. Tolerance of bile duct to intraoperative irradiation. *Surgery* 1982;92:533–40.
- [17] Sindelar WF, Pepper JE, Kinsella TJ, et al. Late effects of intraoperative radiation therapy on retroperitoneal tissues, intestine, and bile duct in a large animal model. *Int J Radiat Oncol Biol Phys* 1994;29:781–8.
- [18] Sindelar WF, Johnstone PA, Hoekstra H, et al. Normal tissue tolerance to IORT: the NCI experimental studies. In: Gunderson LL, Willett CG, Harrison LB, et al., editors. *Intraoperative irradiation: techniques and results*. Totowa, NJ: Humana Press; 1999. p. 131–46.
- [19] Sindelar WF, Kinsella TJ. Studies of intraoperative radiotherapy in carcinoma of the pancreas. *Ann Oncol* 1999;10(Suppl 4):226–30.
- [20] Gillette EL, Gillette SM, Vujaskovic Z, et al. Influence of volume on canine ureters and peripheral nerves irradiated intraoperatively. In: Schildberg FW, Willich N, Kramling H, editors. *Intraoperative radiation therapy: proceedings of the 4th international IORT symposium*. Munich, Germany: Verlag, DieBlauue Eule; 1993. p. 61–3.

- [21] Gillette EL, Gillette SM, Powers BE. Studies at Colorado State University of normal tissue tolerance of beagles to IORT, EBRT or a combination. In: Gunderson LL, Willett CG, Harrison LB, et al., editors. *Intraoperative irradiation: techniques and results*. Totowa (NJ): Humana Press; 1999. p. 147–64.
- [22] Manabe T, Baba N, Ono K, et al. Radical pancreatectomy with intraoperative radiation therapy for pancreatic head cancer. In: Abe M, Takahashi M, editors. *Intraoperative radiation therapy*. Proc. of the 3rd international symposium on intraoperative radiation therapy. New York: Pergamon Press; 1991. p. 249–50.
- [23] Evans DB, Termuhlen PM, Byrd DJ, et al. Intraoperative radiation therapy following pancreaticoduodenectomy. *Ann Surg* 1993;218:54–60.
- [24] Zerbi A, Fossati V, Parolini D. Intraoperative radiation therapy adjuvant to resection in the treatment of pancreatic cancer. *Cancer* 1994;73:2930–5.
- [25] Termuhlen PM, Evans DB, Willett CG. IORT in pancreatic carcinoma. In: Gunderson LL, Willett CG, Harrison LB, Calvo FA, editors. *Intraoperative irradiation*. Totowa: Humana Press; 1999. p. 201–23.
- [26] Valentini V, Morganti AG, Macchia G, et al. Intraoperative radiation therapy in resected pancreatic carcinoma: long-term analysis. *Int J Radiat Oncol Biol Phys* 2008;70:1094–9.
- [27] Calvo FA, Meirino RM, de la Mata MD, et al. Intraoperative radiotherapy. In: Halperin EC, editors. *Principles and practice of radiation oncology*, 5th ed. Philadelphia: Wilkins; 2008. p. 397–406.
- [28] Stephens J, Kuhn J, O'Brien J, et al. Surgical morbidity, mortality, and long-term survival in patients with peripancreatic cancer following pancreaticoduodenectomy. *Am J Surg* 1997;174:600–3.
- [29] Abrams RA and Choo J. Pancreatic cancer. In: Churchill Livingstone, editors. *Clinical radiation oncology*; 2007. p. 1076–77.
- [30] Pisters PW, Abbruzzese JL, Janjan NA, et al. Rapid-fractionation preoperative chemoradiation, pancreaticoduodenectomy, and intraoperative radiation therapy for resectable pancreatic adenocarcinoma. *J Clin Oncol* 1998;16:3843–50.
- [31] Huguet F, André T, Hammel P, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol* 2007;25:326–31.
- [32] Spitz FR, Abbruzzese JL, Lee JE, et al. Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. *J Clin Oncol* 1997;15:928–37.
- [33] Hoffman JP, Lipsitz S, Pisansky T, et al. A Phase II study of preoperative gemcitabine with radiation therapy and chemotherapy for patients with localized, resectable adenocarcinoma of the pancreas. *J Clin Oncol* 1998;16:317–23.
- [34] Lawrence TS, Chang EY, Hahn TM, Hertel LW, Shewach DS. Radiosensitization of pancreatic cancer cells by 2',2'-difluoro-2'-deoxycytidine. *Int J Radiat Oncol Biol Phys* 1996;34:867–72.
- [35] Moore AM, Cardenes H, Johnson CS, et al. A phase II study of gemcitabine in combination with radiation therapy in patients with localized, unresectable, pancreatic cancer: a Hoosier Oncology Group trial. *J Clin Oncol* 2004;22:4105.
- [36] Safran H, King TP, Choy H, et al. Paclitaxel and concurrent radiation for locally advanced pancreatic and gastric cancer. A phase I study. *J Clin Oncol* 1997;15:901–7.
- [37] Boz G, De Paoli A, Roncandin M, et al. Radiation therapy combined with chemotherapy for inoperable pancreatic carcinoma. *Tumori* 1991;77:61–4.