Tumor Response and Patterns of Failure Following Intraoperative Radiotherapy for Unresectable Pancreatic Cancer

Evaluation by Computed Tomography

Shuichi Kanamori, Yasumasa Nishimura, Masaki Kokubo, Keisuke Sasai, Masahiro Hiraoka, Yuta Shibamoto, Ryo Hosotani, Masayuki Imamura and Mitsuyuki Abe

From the Departments of Radiology (S. Kanamori, M. Kokubo, K. Sasai, M. Hiraoka), Oncology, Chest Disease Research Institute (Y. Shibamoto), and First Surgery (R. Hosotani, M. Imamura), Kyoto University, Faculty of Medicine, Kyoto, the Department of Radiology, Kinki University, School of Medicine, Osaka-Sayama, Osaka (Y. Nishimura), and President, Hyogo Medical Center for Adults, Akashi, Hyogo (M. Abe), Japan

Correspondence to: Shuichi Kanamori, MD, Department of Radiology, Faculty of Medicine, Kyoto University, 54-Shogoin-Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan. Tel: 81 75 751 3419. Fax: 81 75 771 9749. E-mail: syuuichi@mbox.kyoto-inet.or.jp

Acta Oncologica Vol. 38, No. 2, pp. 215–220, 1999

Tumor response and patterns of failure following intraoperative radiotherapy (IORT) of 42 patients with unresectable pancreatic cancers were evaluated by computed tomography (CT). At the time of maximum tumor regression, the tumor response rate following IORT was 52%, with three tumors showing CR. The median time of maximum tumor regression was 3 months after IORT. When tumor response was evaluated within 2 months of IORT, no significant difference in survival rate between responders and non-responders was noted. However, when tumor response was evaluated 3–6 months after IORT, the responders showed a significantly better survival rate than the non-responders. Local tumor recurrence, liver metastasis, and peritoneal dissemination were major causes of failure after IORT for unresectable pancreatic cancers. In addition, the median time of detection of these findings by CT was 2–3 months after IORT. Thus, our results indicate that CT performed 3–4 months after IORT is most important for predicting clinical outcome.

Received 20 April 1998
Accepted 3 December 1998

Pancreatic cancer is a devastating disease with a poor prognosis. Despite advances in diagnostic modalities and surgical techniques, most pancreatic cancers are unresectable because of either local tumor invasion or metastatic disease. Intraoperative radiotherapy (IORT) combined with external beam radiotherapy (EBRT) is a promising treatment for unresectable but localized pancreatic cancer (1–7). Although pancreatic cancer is considered radioresistant, computed tomography (CT) of some unresectable pancreatic tumors has revealed significant regression following radiotherapy. However, only a few studies have been evaluated for tumor response in relation to time after IORT, with or without EBRT for unresectable pancreatic cancer (8, 9).

The purpose of this study was to evaluate tumor response and patterns of failure of unresectable pancreatic cancer treated with IORT, with or without EBRT. Because CT is the most common and subjective technique for evaluation of tumor response in pancreatic cancer, we analyzed the CT changes of patients with unresectable pancreatic cancer treated with IORT.

MATERIAL AND METHODS

Patients

Between 1983 and 1995, 70 patients with unresectable pancreatic cancer were treated with IORT, with or without EBRT, at Kyoto University Hospital. Among 70 patients with unresectable pancreatic cancer, 28 patients did not receive CT examinations either before and/or after IORT mainly because of poor general condition or advanced disease, or inability to find CT films. The remaining 42 patients, in whom follow-up CTs had been performed, were analyzed in the present study. The excluded patients included 17 males and 11 females, with a mean age of 62 years.

 ISSN 0284-186X

In Table 1 we present the patient characteristics and treatment parameters for 42 patients with unresectable pancreatic cancers (22 males, 20 females, mean age of 62 years, range: 34–81 years). Pancreatic tumors were located in the head of the pancreas for 23 patients and in the body and tail of the pancreas for 19 patients. At the time of operation, liver metastasis was noted in six tumors, and peritoneal dissemination was observed in one. Clinical stages according to the 1987 UICC staging system were: stage II; 1, stage III; 10, and stage IV; 31.

Of these 42 patients, 37 received IORT combined with EBRT, and 5 patients received IORT alone. Thirty-two patients underwent gastrointestinal and/or biliary bypass procedures, and laparotomy was performed on 10. Histopathological proof of pancreatic adenocarcinomas was obtained for 39 tumors either by needle biopsy of the primary or metastatic tumors, while the remaining 3 tumors were diagnosed as pancreatic cancer by the roentgenological findings and clinical manifestations. All 3 patients in the latter group died of the disease within 17 months of treatment (mean: 11 months), and were thus regarded as having pancreatic cancer and analyzed in this study.

Radiotherapy

The details of techniques and methods used to deliver EBRT and IORT are described elsewhere (1, 6). IORT was delivered using a mean dose of 28.3 Gy (range, 12–33 Gy) by 12–20 MeV electrons, according to the depth of the tumor. The applicators most frequently used were 5–7 cm in diameter. The IORT field covered the gross tumor volume with minimal margin, not generally including the gastrointestinal tract. The field-in-field method was used for patients in whom inclusion of the gastrointestinal tract was deemed necessary, as is the case with unresectable pancreatic head cancer. Briefly, 12 Gy was delivered over a large field including the tract, and the rest of the IORT dose (usually 18 Gy) was delivered to a smaller field excluding the tract. This field-in-field method of IORT was performed on 13 patients.

External beam radiotherapy was delivered with a mean dose of 44.0 Gy (range, 30–60 Gy) with a fraction size of 1.7–1.8 Gy. The energy of EBRT was 10 or 15 MV x-rays from linear accelerators, mostly using three portals from the anterior, left, and right directions. The EBRT field encompassed the tumor plus a 2-cm margin, with average field sizes of 10×10 cm from the anterior direction and 10×7 cm from the lateral directions. Thirty-seven patients were treated with IORT (mean dose: 28.6 Gy) combined with EBRT (mean dose: 45.2 Gy), while the remaining 5 patients were treated with IORT alone (mean dose: 26.0 Gy). Mean radiotherapy doses according to radiotherapy modalities are also presented in Table 2.

Table 1

Patients' characteristics and treatment parameters for unresectable pancreatic cancer

Sex	M : F = 22:20
Age	Mean. 62 years (range 34–81)
UICC Stage	II : III : VI = 1: 10 : 31
Location	Head : body = 23 : 19
Bypass	(+) : (−) = 32 : 10
i.a. Chemo.	(+) : (−) = 9 : 33

Chemotherapy

Since 1989, intra-arterial (i.a.) infusion chemotherapy has been performed on patients with unresectable pancreatic cancer, and 9 patients in the present analysis were treated with i.a. infusional chemotherapy. At operation, a catheter was inserted retrogradely into the left gastric or the splenic artery, with an infusion port installed subcutaneously in the abdominal wall. Chemotherapeutic agents were injected every 2–4 weeks during or after postoperative EBRT for 6–12 months, or until death. Various combinations of mitomycin C (2–8 mg), epirubicin (10–30 mg), 5-fluorouracil (5-FU, 250–500 mg), or *cis*-platinum (10–50 mg) were administered.

CT examinations

A total of 163 CT examinations of the 42 patients was evaluated; 82 examinations were performed before IORT, while 81 were performed after IORT. Scan thickness and intervals were 10 mm (72%) or 5 mm (28%). Intravenous contrast enhancement was performed in 146 examinations (90%).

Tumor response was evaluated according to the time between IORT and CT examination. For 35 patients, CT examinations were performed within 2 months of IORT, for 18 patients examinations were conducted between 3 and 6 months, and for the remaining 9 patients between 7 and 12 months (see Table 3). As local tumor recurrence, liver metastasis, and peritoneal dissemination were major causes of failure after IORT for 42 unresectable pancreatic cancers, the CT changes analyzed were: (i) tumor regression, (ii) local recurrence in the IORT field, (iii) liver metastasis, and (iv) peritoneal dissemination. To evaluate

Table 2

Tumor response rate according to the modalities of radiotherapy

	No.	IORT/EBRT* (Gy)	CR + PR (%)
IORT + pre EBRT	10	27.5/37.5	5 (50%)
IORT + post EBRT	8	27.9/40.8	7 (87%)
IORT + pre & post EBRT	19	30.7/51.2	9 (47%)
IORT alone	5	26.0/0	1 (20%)

* Mean radiation dose.

Table 3

Tumor response rates according to timing of CT examination

Timing	No.	CR + PR (%)
0–2 months after IORT	35	10 (28%)*
3–6 months after IORT	18	13 (72%)*
7–12 months after IORT	9	7 (77%)

* Difference between the groups was significant ($p < 0.01$).

the tumor regression, tumor volume was compared with the pretreatment volume. Grades of tumor response were as follows: complete tumor regression was designated as CR (complete response), 50–99% tumor regression as PR (partial response), less than 50% tumor regression as NC (no change), and progressive disease as PD. In this study, patients showing CR or PR were regarded as responders, and those showing NC or PD as non-responders. The criterion of local recurrence in the IORT field was tumor progression in the form of enlarged tumor size in the IORT field, and that of peritoneal dissemination was the existence of ascites with or without paraaortic adenopathy on CT.

Statistical analysis

Overall survival rate was calculated from the day of IORT. Statistical analysis between survival curves plotted using the Kaplan–Meier method was assessed by the logrank test. The χ^2-test with Yates' correction and the Student's t-test were used to evaluate the differences in treatment parameters and response rates.

RESULTS

For the 42 patients analyzed, the median survival time (MST) was 6.5 months, with a 5-year survival rate of 5%, whereas the MST for the 28 patients excluded from the present analysis was 4 months. The 42 patients included in the study had a significantly better overall probability of survival than the 28 patients excluded ($p < 0.01$). In terms of complications, none of the 42 patients died within one month of surgery. Gastrointestinal ulcers and duodenal stenosis were noted in 4 and 3 patients, respectively. Intestinal perforation was observed in one patient with gastric ulcers 17 months after IORT. The details of the complications associated with IORT have been reported previously (1).

Among the 42 unresectable pancreatic cancers treated with IORT, no significant difference in survival probability was observed in terms of the administration of chemotherapeutic agents. The MST of the 9 patients treated with i.a. chemotherapy was 7 months, and that of the remaining 33 patients treated without i.a. chemotherapy was also 7 months.

At the time of maximum tumor regression, tumor response was 3 CR, 19 PR, 11 NC, and 9 PD; the overall tumor response rate (CR + PR) was 52% (22/42). The survival curves for the 22 responders and the 20 non-responders are shown in Fig. 1. The MST rates of the responders (CR + PR) and the non-responders (NC + PD) were 7 months and 3 months, respectively. Difference between the survival curves was significant ($p < 0.005$). The median time to maximal tumor regression was 3 months (range, 1–10 months) after IORT. Table 2 shows the tumor response rates according to treatment modalities. The tumor response rates in the IORT + EBRT groups (47–87%) were higher than those in the IORT group (20%), although the difference in response rate was not significant. This result suggests a beneficial effect of IORT + EBRT compared with IORT alone.

Tumor response rate according to interval following IORT was evaluated (Table 3). The tumor response rate within 2 months of IORT was 28% (10/35), increasing to 72% (13/18) at 3–6 months, and 77% (7/9) at 7–12 months. The tumor response rate at 3–6 months is significantly higher than that within 2 months ($p < 0.01$). Fig. 2 shows the survival curves according to tumor response evaluated (a) within 2 months of IORT, and (b) 3–6 months after IORT. When evaluation of tumor response was performed within 2 months, no significant difference in survival curves was observed between the responders and the non-responders. However, when the tumor response was evaluated by CT 3–6 months after IORT, the survival curve of the responders was significantly better than that of the non-responders ($p < 0.05$).

An intratumoral low-density area (LDA) was noted in 10 tumors of pretreatment CT. For the remaining 32 patients, the appearance of intratumoral LDA following IORT was evaluated in the follow-up CTs. In addition to the tumor regression, intratumoral LDA was observed in 22% (7/32) of the tumors, and the median time to appearance was 4 months. No significant difference in survival rates was observed between the patients whose tumor showed intratumoral LDA and those who did not.

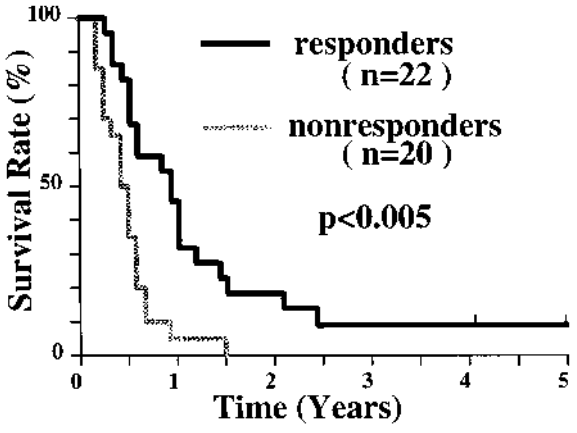

Fig. 1. Survival curves for the 22 responders (CR + PR) and the 20 non-responders (NC + PD). Tumor response was evaluated at the maximum regression.

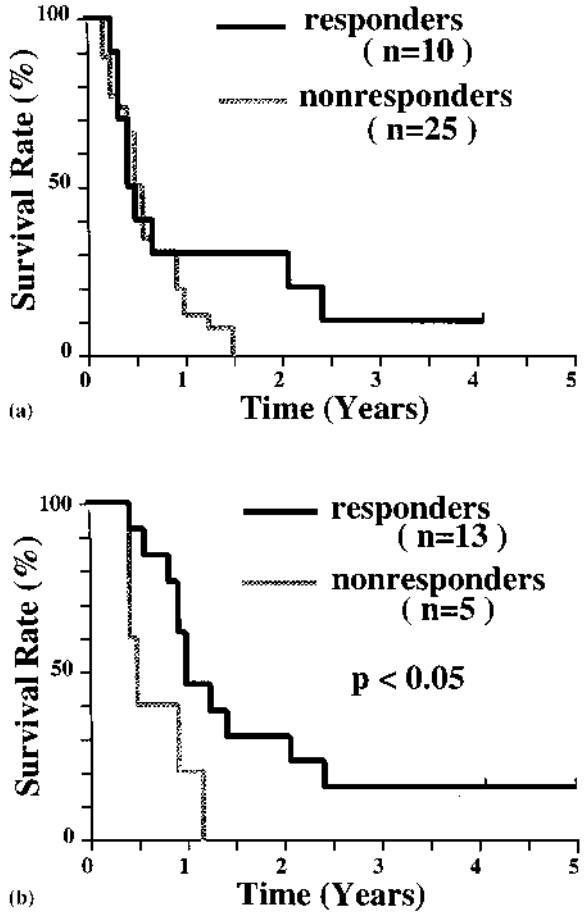

Fig. 2. (a) Survival curves for 35 patients according to tumor response evaluated within 2 months of IORT. (b) Survival curves for 18 patients according to tumor response evaluated between 3 and 6 months after IORT.

Table 4 shows patterns of failure after IORT for unresectable pancreatic cancers. Including the 9 PD patients, local recurrence in the IORT field was noted in 33% (14/42) of the tumors. The median time interval between IORT and tumor regrowth was 2 months (range, 1–23 months). Among the 22 responsive patients, tumor regrowth was observed in 5 patients, and the median time of appearance was 7 months (2–23 months). Two of the 3 CR cases did not show local recurrence or metastasis during the follow-up period of 173 and 80 months, while one tumor recurred 23 months after IORT. In this study, local tumor recurrence, liver metastasis, and peritoneal dissemination were noted as major causes of failure after IORT for 42 unresectable pancreatic cancers. Liver metastasis was noted in 6 patients (14%) at the time of operation. Among the remaining 36 patients, liver metastasis developed after IORT in 22% (8/36), and the median time of detection of liver metastasis by CT was 3 months (range, 1–26 months) after IORT. Peritoneal dissemination was detected in one patient at the time of operation. Among the remaining 41 patients, peritoneal dissemination was noted in 21% (9/41), and the median time of detection of peritoneal dissemination by CT was 2 months (1–6 months) after IORT. Median times of local recurrence and distant metastasis were 2–3 months, indicating that CT performed 3 months after IORT reveals approximately 50% of local recurrence and distant metastasis for unresectable but localized pancreatic cancer.

Table 4

Tumor response and patterns of failure

	No.	Time* (range)
Tumor regression	22/42 (52%)	3 months (1–11)
Liver metastasis	8/36 (22%)	3 months (1–26)
Peritoneal dissemination	9/41 (21%)	2 months (1–6)
Local rec. in IORT field	14/42 (33%)	2 months (1–23)

* Median time of manifestation on CT following IORT.

The serial CT scans of a typical tumor response after IORT combined with preoperative EBRT are shown in Fig. 3. Although no tumor regression was observed 1 month after IORT, the tumor had regressed significantly at 4 months. No further tumor regression was observed on the CT obtained at 7 months. However, liver metastasis had developed at 7 months, causing death 12 months after IORT without local recurrence of the primary tumor.

DISCUSSION

Pancreatic cancer is considered to be a highly radioresistant tumor. In the present study, 52% of the unresectable pancreatic tumors regressed by more than 50% in volume after IORT, with or without EBRT. However, the overall response rate might in fact be lower than 50%, as CT was not performed on 28 patients because of poor general condition or advanced disease, and who are thus excluded from this study. Thus, the local control of unresectable pancreatic cancer is quite difficult even by high dose IORT combined with EBRT.

In the analysis of the time interval between IORT and maximal tumor regression, maximal tumor regression took place at approximately 3 months after treatment. Thus, tumor regression of unresectable pancreatic cancer can be said to be slow. When tumor response was evaluated by CT 3–6 months after IORT, the survival rate of the responders was significantly higher than that of the non-responders ($p < 0.05$, Fig. 2). Only a few papers have reported CT changes after IORT for pancreatic cancer (8, 9). Nishimura et al. (8) evaluated CT changes after IORT for unresectable pancreatic cancer, and found that all of 7 tumors regressed slowly during the first few months after IORT. However, the time interval between IORT and the maximal tumor regression could not be estimated in their study because of the lack of long-term CT follow-up after treatment. Quivey et al. (9) reported initial local tumor regression in more than 80% of 16 pancreatic cancers

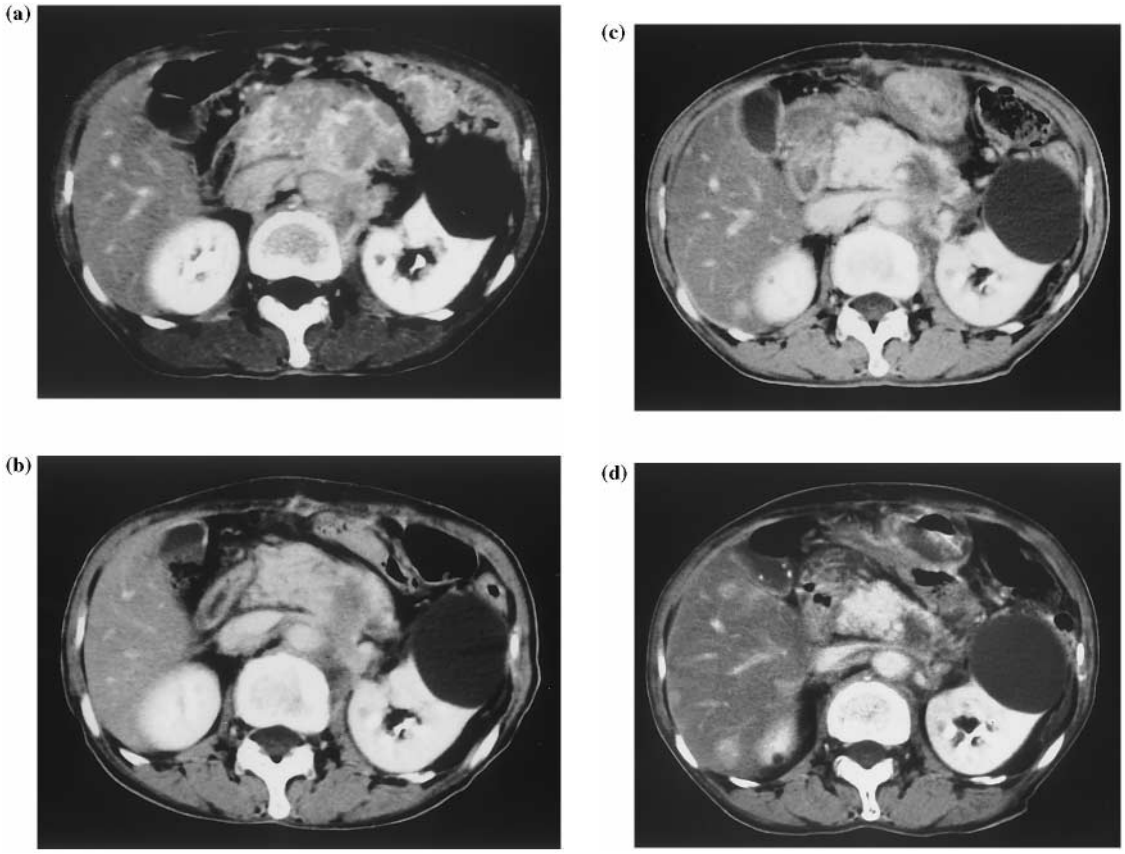

Fig. 3. This 71-year-old female patient with adenocarcinoma in the pancreatic body was treated with preoperative EBRT (41.4 Gy) and IORT (20 MeV, 30 Gy). Typical tumor regression was noted in these serial CT images. (a) Pretreatment CT scan. The huge tumor in pancreatic body and tail was noted. (b) One month after IORT: tumor regression was not evident. (c) Four months after IORT: significant tumor regression was noted. (d) Seven months after IORT, the tumor volume was the same as that at 4 months after IORT. Liver metastasis was noted at this time.

following heavily charged particle radiotherapy. In addition, they reported tumor progression on CT to be correlated with clinical progression in more than 90% of the patients. Bruckner et al. (10) reported the tumor responses of 20 unresectable pancreatic cancers treated with chemoradiotherapy, with an overall response rate of 55% evaluated by CT, and 7 tumors showing complete response. They observed complete tumor regression between 3 and 6 months after completion of treatment. These results were consistent with our own in terms of the slow pace of tumor regression. In the present study, responders showed a significantly better clinical outcome than non-responders; 2 of the 3 CR responders survived for 5 years.

Intratumoral LDA was noted in 22% (7/32) of our patients, with a median interval of 4 months. Nishimura et al. (8) and Hoekstra et al. (11) showed necrosis and fibrosis to be the most frequent histopathological changes following IORT, and this intratumoral LDA may be necrosis and/or fibrosis after IORT + EBRT. Although the appearance of LDA may be a factor of tumor response, no significant difference was noted in the survival rate of patients in the present study.

Tumor response rates according to treatment modality are presented in Table 2. The tumor response rate of the 37 patients treated with IORT + EBRT was 57% (21/37), while that of patients on IORT alone was 20% (1/5). The superiority of IORT + EBRT over IORT alone for unresectable pancreatic cancer has been previously reported (3, 5, 12), and our current treatment policy is to perform IORT plus EBRT whenever possible for patients without distant metastasis.

The incidence of liver metastasis in pancreatic cancer patients is suggested to be approximately 50% (8, 13, 14). Garton et al. (14) reported an approximate 5-year survival rate (7%), with incidences of local failure (20%), liver metastasis (30%), and peritoneal seeding (33%) following treatment of pancreatic cancer with IORT + EBRT. In the present analysis, local tumor recurrence, liver metastasis, and peritoneal dissemination were detected in 33%, 22%, and 21% of the patients, although the fact that some patients were excluded from the study may mean that the real failure rates are higher than these results. As the median times of the appearance of both local failure and distant metastasis are at 2–3 months after IORT, prog-

noses for patients with unresectable pancreatic cancer may be predictable by a CT scan obtained 3–4 months after IORT.

CONCLUSIONS

Our results show that IORT can induce at least a radiological tumor response for unresectable pancreatic cancers. Tumor response, local failures, and distant metastasis were frequently detected within a few months after IORT. The most important result is the fact that we should not perform our evaluation for response too soon after completed irradiation. Thus, CT evaluation of the tumor response for unresectable pancreatic cancer should be carried out 3–4 months after IORT.

REFERENCES

1. Nishimura Y, Hosotani R, Shibamoto Y, et al. External and intraoperative radiotherapy for resectable and unresectable pancreatic cancer; analysis of survival rates and complications. Int J Radiat Oncol Biol Phys 1997; 39: 39–49.
2. Abe M, Takahashi M. Intraoperative radiotherapy: Japanese experience. Int J Radiat Oncol Biol Phys 1981; 7: 863–8.
3. Abe M, Shibamoto Y, Takahashi M, Manabe T, Tobe T, Inamoto T. Intraoperative radiotherapy in carcinoma of the stomach and pancreas. World J Surg 1987; 11: 459–64.
4. Kawamura M, Kataoka M, Fujii T, et al. Electron beam intraoperative radiation therapy (EBIORT) for localized pancreatic carcinoma. Int J Radiat Oncol Biol Phys 1992; 23: 751–7.
5. Roldan GE, Gunderson LL, Nagorney DM, et al. External beam versus intraoperative and external beam irradiation for locally advanced pancreatic cancer. Cancer 1988; 61: 1110–6.
6. Shibamoto Y, Manabe T, Ohshio G, et al. High-dose intraoperative radiotherapy for unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys 1996; 34: 57–63.
7. Tepper JE, Noyes D, Krall JM, et al. Intraoperative radiation therapy of pancreatic carcinoma: a report of RTOG-8505. Int J Radiat Oncol Biol Phys 1991; 21: 1145–9.
8. Nishimura A, Itoh I, Mouri I, et al. Computed tomography in the assessment of pancreatic tumor response after intraoperative radiotherapy. Acta Radiol Oncol 1988; 6: 85–91.
9. Quivey JM, Castro JR, Chen GT, Moss A, Marks WM. Computerized tomography in the quantitative assessment of tumour response. Br J Cancer 1980; 41 (Suppl): 30–4.
10. Bruckner HW, Kalnichi S, Dalton J, et al. Combined modality therapy increasing local control of pancreatic cancer. Cancer Invest 1993; 241–6.
11. Hoekstra HJ, Restrepo C, Kinsella TJ, Sindelar WF. Histopathological effects of intraoperative radiotherapy on pancreas and adjacent tissues: a postmortem analysis. J Surg Oncol 1988; 37: 104–8.
12. Fossati V, Cattaneo GM, Zerbi A, et al. The role of intraoperative therapy by electron beam and combination of adjuvant chemotherapy and external radiotherapy in carcinoma of the pancreas. Tumori 1995; 81: 23–31.
13. Evans DB, Abbruzzese JL, Cleary KR, et al. Preoperative chemoradiation for adenocarcinoma of the pancreas: excessive toxicity of prophylactic hepatic irradiation. Int J Radiat Oncol Biol Phys 1995; 33: 913–8.
14. Garton GR, Gunderson LL, Nagorney DM, et al. High-dose preoperative external beam and intraoperative irradiation for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 1993; 27: 1153–7.