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INTRAOPERATIVE RADIOTHERAPY IN THE MULTIDISCIPLINARY TREATMENT OF PEDIATRIC TUMORS

A preliminary report on initial results

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Abstract

From September 1984 to July 1987, 33 children received intraoperative radiotherapy as part of a multidisciplinary tumor treatment. Their age ranged from 2 to 17 years. Tumors types: Ewing's sarcoma (n=11), osteosarcoma (n=8), soft tissue sarcomas (n=5), Wilms' tumor (n=3), neuroblastoma (n=3), malignant pheochromocytoma (n=1), Hodgkin's disease (n=1), and optic nerve glioma (n=1). In 25 patients the disease was localized while 8 had distant metastases. Intraoperative radiotherapy was used in 26 previously untreated patients as part of a radical treatment program and in 7 cases as an effort to rescue local failures (5 in previously irradiated areas). The intraoperative radiation field included the surgically exposed tumor or tumor bed, and the single doses ranged from 10 to 20 Gy, with 6–20 MeV electrons. Patients with osteosarcoma and recurrent tumor in a previously irradiated area did not receive postoperative external beam radiotherapy. With a median follow-up time of 10 months (1 to 31+months) 24 out of 33 patients are alive without local recurrence and 9 have died from tumor (5 with local disease progression). Intraoperative radiotherapy seems to be a feasible treatment which might promote local control in pediatric tumors.

Key words: Pediatric tumors, intraoperative radiotherapy, results, side effects.

In intraoperative radiotherapy (IORT) a high single radiation dose is delivered to a surgically defined area, with protection of normal uninvolved organs and tissues (1).

IORT may increase the therapeutic index by delimitation of local tumor spread, sparing of normal uninvolved tissues, and an increase of the biological efficacy of the irradiation after surgical debulking (2).

Since the early 1960's Japanese investigators have collected an important amount of information on IORT with fast electrons in different neoplasms of adult patients (1, 3). Since the late 1970's this modality has also been used in Western countries, and in the USA investigators have developed programs including IORT for abdominal and pelvic tumors (4). Reports about the use of IORT in pediatric tumors are still quite few (5–7).

Candidates for IORT in children could be patients with locally advanced tumors with high local relapse rate and radioresponsive histology. IORT is also an attractive alternative for patients in whom external beam therapy can be expected to induce a high rate of late radiation sequlae (8).

The IORT program of the University Clinic of Navarra, started in 1984 as a clinical research project. IORT has been used as a boost in addition to conventional external beam radiotherapy in most cases. The preliminary data from our IORT program have now been analyzed with special emphasis on the feasibility of the technique, toxicities and complications observed, and local tumor control rates.

Material and Methods

Some institutional requirements are needed for IORT as manufacture of specially designed treatment cones, calibration of these devices and accomodation of a linear accelerator room as a surgical theatre.

From the clinical point of view a consensus must be reached between surgeons and clinical oncologists in order to discuss therapeutic alternatives for locally advanced tumors and select candidates for IORT. Good coordination is necessary, because the treatment of each case requires collaboration of anestesiologists, surgeons, radiotherapists, physicists and nurses (9).

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Table 1
Ewing's sarcoma

Primary location	Patients n	Median follow-up months	Local control	Patients alive
Axial bones				
No previous treatment	2	20	1/2	1/2
Local recurrence after previous treatment	1		1/1	0/1
Extremities				
No previous treatmet	6	16	6/6	6/6
Recurrence	2		2/2	1/2
Total	11	18	10/11	8/11

A total of 33 patients have been treated from 1984 to 1987, presenting 8 different tumor types; 11 Ewing's sarcomas, 8 osteosarcomas, 5 soft tissue sarcomas, 3 neuroblastomas, 3 Wilms' tumors, 1 Hodgkin's disease, 1 pheochromocytoma and 1 glioma. The median age was 10 years (range 2 to 17 years). There were 20 males and 13 females.

The primary tumors were located in the extremities in 20 cases, retroperitoneum in 5, vertebra in 3, small pelvis in 3 and intracranially in 2 cases.

In 25 patients the disease was localized while 8 patients had evidence of distant metastases. IORT was used in 26 previously untreated patients as part of a radical treatment program, and in 7 patients as an effort to rescue local failures (5 in previously irradiation areas).

The IORT field included in all cases the surgically exposed tumor or tumor bed. The delivered single dose ranged from 10 to 20 Gy, given with 6–20 MeV electron beams.

Chemotherapy for all Ewing's sarcoma patients (primary or recurrent disease) was given according to the T11 Rosen regimen (10).

Chemotherapy in osteosarcoma patients consisted of neoadjuvant intraarterial cisplatinum and intravenous doxorubicin (11), followed by local treatment and systemic adjuvant or therapeutic multiagent chemotherapy as described by Rosen et al. (12).

Results

The results in 4 different tumor groups have been analyzed: Ewing's sarcoma, osteosarcoma, soft tissue sarcoma, and a group with miscellaneous tumors.

Ewing's sarcoma. The previously untreated patients (n=6) started with systemic chemotherapy (1 cycle) and external beam radiotherapy with total tumor doses of 40–50 Gy in 5 weeks, followed by partial or total surgical resection of the involved bone and surrounding affected tissues plus IORT 10–15 Gy in the tumor bed. Treatment was completed with systemic chemotherapy, according to the T11 protocol of Rosen (10).

Table 2
Osteosarcoma

Disease stage	Patients n	Median follow-up months	Local control	Patient alive
Localized	4		4/4	3/4
Metastatic	4		4/4	3/4
Total	8	12	8/8	6/8

Table 3
Soft tissue sarcomas

Tumor location	Patients n	Median follow-up months	Local control	Patient alive
Pelvis	1		0/1	0/1
Extremities	4		3/4	4/4
Total	5	13	3/5	4/5

Patients with local recurrence (n=3) received reinduction systemic chemotherapy (1 to 2 cycles), followed by surgical resection of bone and surrounding tissues plus IORT boost of 20 Gy single dose in the tumor bed. The treatment was continued by systemic chemotherapy.

The preliminary results are shown in Table 1. The median follow-up time of the entire group is at present 18 months and the local control rate 90% (November 1987). Only one patient relapsed locally (paravertebral area). Three patients died from progressive metastatic disease.

Concerning the IORT related side effects 3 patients developed soft tissue necrosis, and 2 patients mild to moderate soft tissue fibrosis.

Osteosarcoma. These patients started with intraarterial cisplatinum and intravenous doxorubicin for 3 courses, followed by surgical 'en bloc' resection of the bone tumor

Table 4

IORT results in miscellaneous group

Tumor site	Patients n	Histology	Subsequent ext. irradiat.	Chemotherapy	Follow-up months	Local control	Patient status
CNS	2	Glioma	+	−	28	+	AWD
		Neuroblastoma	+	+	8	−	DWD
Vertebral	1	Metastatic Wilm's	+	+	30	+	AWD
Upper abdomen	5	Hodgkin's	−	−	23	+	NED
		Wilms' (stage II)	−	+	29	+	NED
		Wilms' (stage II)	−	+	20	+	NED
		Neuroblastoma (s. IV)	+	+	14	−	DWD
		Pheochromocytoma	−	+	31	+	NED
Pelvic	1	Neuroblastoma (s. III)	−	+	24	+	DWD

AWD = Alive with disease. DWD = Dead with disease. NED = No evidence of disease.

and involved tissues plus IORT 20 Gy in the tumor bed. Treatment was completed with systemic adjuvant chemotherapy during one year. All 8 cases had involvement of surrounding soft tissues. In 4 patients, lung metastases were present when the treatment started.

All patients are still locally controlled with a median follow-up time of 12 months. Two patients died from metastatic progressive disease (Table 2).

IORT related toxicity in this group has been peripheral neuropathy in one patient, and moderate non-symptomatic soft tissue fibrosis in two additional patients.

Soft tissue sarcomas. The treatment in soft tissue sarcomas started with systemic and intraarterial chemotherapy followed by tumor resection plus 10–15 Gy of IORT in the tumor bed or in the residual disease area. External beam radiotherapy was subsequently given, with total doses of 46–50 Gy in 5 weeks.

Table 3 shows the results. The median follow-up time for this group is at present 13 months. Three of the 5 patients are still locally controlled. One failure was seen in a massive pelvic primary with spilling of the tumor during surgery and another failure occurred in the margin of the external beam field.

Toxicity related to IORT has been one case of moderate soft tissue fibrosis and one case of peripheral neurophathy.

Miscellaneous group. In this group the patients were treated according to different conventional methods depending upon the tumor histology. In general, maximal surgical resection was aimed at with addition of IORT 10–15 Gy to tumor bed, or 15–20 Gy to macroscopic residual disease areas. Additional postoperative therapy was given when indicated.

In Table 4, tumor sites and histological types are shown. As indicated, in certain patients subsequent treatment (external beam radiotherapy and/or chemotherapy) was omitted after surgery and IORT.

Seven of the 9 patients have attained local control and are alive with no evidence of disease. The follow-up time ranges from 8 to 31 months.

Discussion

IORT has stimulated surgical and radiation oncology groups around the world (13–15). Data suggesting high local control rates have been reported in advanced colorectal (16) and pancreatic cancer (17), in soft tissue sarcomas (1), and in gastric cancer (18). Survival benefit has been suggested in a report on gastric cancer (19). IORT has also been explored with interesting results in prostatic (20) and bladder carcinoma (21). In adult oncology IORT investigators have organized phase I–II multiinstitutional trials (22) and recently a consensus meeting recommended phase III trials with IORT in selected colorectal cancers (23).

For pediatric oncology IORT is an interesting alternative to extensive external beam radiotherapy in an effort to decrease long-term side effects. It is also a suitable modality for the delivery of a boost dose. Normal tissue tolerance and complications of IORT should be carefully considered when using IORT in pediatric patients (24, 25). Recommendations about quality control in clinical trials using IORT should be closely followed when protocols for pediatric tumors are designed (26).

In our experience, IORT is technically feasible in pediatric patients with locally advanced tumors. No immediate postoperative complications were related to IORT procedure. Single doses of 10 to 15 Gy can be safely given to extremities, head and neck, abdomen and pelvis. However, when additional postoperative radiation therapy is given at doses of 45–50 Gy in 5 weeks, there is a substantial increase of toxicity as local necrosis, neuropathy and soft tissue fibrosis. Peripheral nerves are vulnerable to high single doses of fast electrons as employed in IORT (27). Animal studies have shown severe neuropathic changes following IORT 20 Gy. Neuropathy after irradiation has been reported in patients with retroperitoneal tumors (28). In our study peripheral nerve damage was observed with a similar clinical pattern as described previously in IORT patients.

IORT seems to promote control of locally advanced tumors not amenable to complete surgical excision. The

observation time, however, is still short and our series of patients rather small. Further studies are needed in order to evaluate the role of IORT in pediatric tumors.

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