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Original research article

Intraoperative radiation therapy opportunities for clinical practice normalization: Data recording and innovative development

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ABSTRACT

Background: Intraoperative radiotherapy (IORT) refers to the delivery of a high dose of radiation at the time of surgery.
Aim: To analyze clinical and research-oriented innovative activities developed in a 17-year period using intraoperative electron-radiation therapy (IOeRT) as a component of treatment in a multidisciplinary approach for cancer management.
Materials and methods: From 01/1995 to 03/2012 IOeRT procedures were registered in a specific Hospital-based database. Research and developments in imaging and recording for treatment planning implementation are active since 2006.
Results: 1004 patients were treated and 1036 IORT procedures completed. Median age of patients was 61 (range 5 months to 94 years). Gender distribution was male in 54% of cases and female in 46%. Disease status at the time of IORT was 796 (77%) primary and 240 (23%) recurrent. Cancer type distribution included: 62% gastrointestinal, 18% sarcoma, 5% pancreas, 2% paediatric, 3% breast, 77 7% oligotopic recurrences, 2% other. IORT technical characteristics were: Applicator size 5 cm 22%, 6 cm 21%, 7 cm 21%, 8 cm 15%, 9 cm 6%, 10 cm 7% 12 cm 5% 15 cm 3%. Electron energies: 6 MeV 19%, 8 MeV 15%, 10 MeV 15%, 12 MeV 23%, 15 MeV 19%, 18 MeV 6%, other 3%. Multiple fields: 108 (11%). Dose: 7.5 Gy 3%, 10 Gy 35%, 12 Gy 3%, 12.5 Gy 49%, 15 Gy 5%, other 5%.

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Conclusion: An IORT programme developed in an Academic Hospital based on practice-oriented medical decisions is an attractive interdisciplinary oncology initiative proven to be able to generate an intensive clinical activity for cancer patient quality care and a competitive source of scientific patient-oriented research, development and innovation.

1. Background

Intraoperative radiotherapy (IORT) refers to the delivery of a high dose of radiation at the time of surgical intervention. IORT achieves highly effective radiation doses to a specific target while dose-limiting healthy structures are surgically displaced or shielded. This procedure uses a multidisciplinary approach in the treatment of cancer emphasizing an interaction between surgery and radiotherapy by minimizing surgical residue, maximizing the radiobiological effects of a single high dose of radiation and optimizing the duration of the treatment.[1]

The modern approach to IORT began in the early 60 s with studies by Abe at the University of Kyoto using single high dose of gamma-rays of cobalt unit and electrons of betatron. In 1970, special IOERT facilities with in-room conventional linear accelerators were equipped at the Howard University Hospital and the Massachusetts General Hospital. In the early 90s, dedicated mobile electron linear accelerators and a miniaturized low-energy X-rays machine were introduced to the clinical practice in a number of radiotherapy centres worldwide.[2]

2. Aim

This article aims to report the data collected by a database registry from 17 years of experience in performing this procedure in an Academic European Hospital (Hospital General Universitario Gregorio Marañón, Madrid, Spain) with particular focus on clinical and technical aspects of IORT treatments. The type of IORT programme developed in this institution involves the application of electron beams. Two non-dedicated fixed linear accelerators are available, requiring transportation from the operating room to the accelerator in all procedures. In this time-frame several research projects have been implemented to extend technological knowledge for treatment planning.[3]

3. Materials and methods

From 01/1995 to 03/2012 IORT procedures were recorded in a specific database registry where real-time or retrospective data was entered. Information was integrated in order to analyze clinical and technical parameters of the treatment programmes including the IORT component. The data-base registered the following demographic, clinical and technical information: (a) anonymized patient data including age, gender, performance status according to Karnofsky scale; (b) tumour data including site, histology, grading, staging according to TNM classification, primary or recurrent tumour status at IORT evaluation; (c) treatment data including treatment intent, extension of surgery, data of surgery and treatment strategy; (d) specific IORT data included IORT use prior/after tumour removal, number of fields, applicator diameter and bevel angle, energy and type of radiation, radiotherapy device, total dose, use of bolus, reference isodose. Data collection for the purpose of the present analysis ended in March 2012.

4. Results

Since 1995, data from 1036 procedures were collected and 1004 patients were treated. Median age of patients was 61 ranging 5 months to 94 years. Gender distribution was male in 54% of cases and female in 46%. Cancer site and disease status at the time of IORT was 796 (77%) primary and 240 (23%) recurrent. The intent of the treatment was curative in 98% of the cases and palliative in 2%. Cancer type distribution was: Gastro-intestinal 641 (62%) (including 553 (53%) colorectal and 88 (9%) esophago-gastric), 190 (18%) sarcoma, 55 (5%) pancreas, 19 (2%) paediatric, 31 (3%) breast, 77 (7%) oligotopic recurrences, 23 (2%) other. The following tumour sites/histologies are included in the last two categories in order of frequency: gynaecologic (cervix, endometrium, ovary, vagina, vulva), urologic (kidney, bladder, testicle), keloid, chordoma, hepatobiliary, adrenal, lymphoma, schwanoma, sacroiliac thyroid metastases, spleen.

The type of surgery performed involved radical residue in 89% of the cases, microscopic residue in 3%, macroscopic residue in 7% and no resection in 1% of the cases. Rectal cancer and sarcomas, because of the large number of patients treated, are the tumours that most frequently received each type of surgery whereas pancreatic and cervix cancers were the most commonly treated after a non resective intervention. The collaborating surgical specialties and their rate of involvement are the following: General Surgeons 76%, Orthopaedic Surgeons 12%, Gynaecologists 8%, Paediatric Surgeons 2%, Urologists 1% and Dermatologists 1%.

IORT technical characteristics included the following items: (a) Applicator size: 5 cm 22%, 6 cm 21%, 7 cm 21%, 8 cm 15%, 9 cm 6%, 10 cm 7% 12 cm 5% 15 cm 3%.

(b) Electron energies: 6 MeV 19%, 8 MeV 15%, 10 MeV 15%, 12 MeV 23%, 15 MeV 19%, 18 MeV 6%, other 3%. (c) Multiple fields: 108 (11%). (d) Dose: 7.5 Gy 3%, 10 Gy 35%, 12 Gy 3%, 12.5 Gy 49%, 15 Gy 5%, other 5%.

Cancellation rate is estimated at 15%. Anaesthesia time ranged from 1 h to 14 h, median 4 h. Median IORT time (including transportation) was 50 min (range 20–120 min).

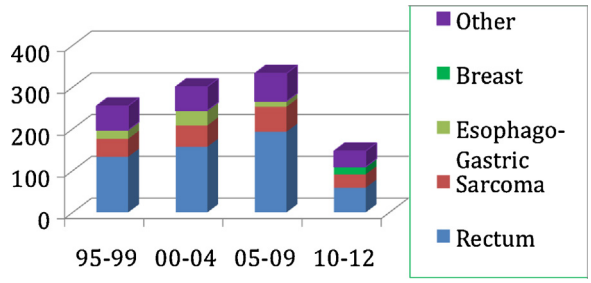

Fig. 1 – Institutional 5-years period analysis of the IORT programme: cancer sites.

4.1. *Institutional activity: indications vs. time*

Fig. 1 describes the total performance and types of cancer in the IORT programme along the 17 years of activity in 5-year periods. This activity has proven to be stable.

From 1995 to 1999: 255 IORT treatments were performed. Median age was 61 years with a range from 5 months to 94 years. Gender distribution during this period was male in 57% of the cases and female in 43%. The most prevalent tumours were rectum in 52%, sarcoma in 17%, and esophago-gastric in 8%.

From 2000 to 2004: 301 patients were treated. Median age of the patients was 58 years (range 1–80 years). Gender distribution was male in 60% and female in 30% of the cases. The most treated tumours types were rectum in 52%, sarcoma in 17% and esophago-gastric in 12%.

From 2005 to 2009: 333 IORT procedures were performed. Median age was 63 years with a range from 8 months to 88 years. Gender distribution was male in 52% and female in 48%. The most frequently treated tumours were rectum in 58%, sarcomas in 18% and esophago-gastric in 4%.

From 2010 to 2012: 147 patients received IORT treatments. Median age was 62 years (range 2–85 years). Gender distribution was female in 58% and male in 42%. The most prevalent tumours were rectum in 40%, sarcoma 22% and breast in 12%.

4.2. *Technical characteristics of IORT: correlations with cancer sites and status*

A description of applicator (Fig. 2), energy (Fig. 3) and dose (Fig. 4) performance in common IOERT indications. A specific analysis of IOERT technical characteristics is described for the dominant diseases treated (Tables 1 and 2).

5. Discussion

The interest of the survey involved the understanding that prospective registry of data is an optimized clinical practice and can lead to promote quality in the development of this treatment modality.

Following a general review of the data obtained, it is stressed that the intent of the delivered treatments is almost exclusively curative and that in a high percentage the disease status at the time of IORT is primary at the time of initial

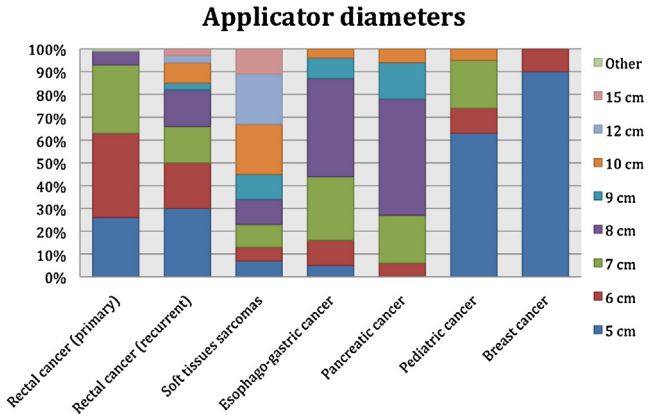

Fig. 2 – Cancer site vs. applicator diameter selected in technical common indications of IOERT.

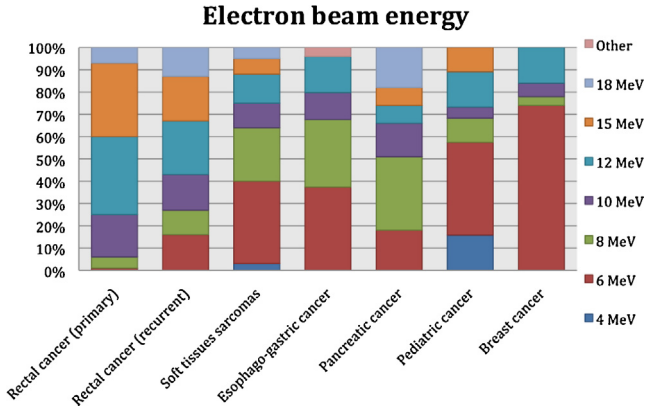

Fig. 3 – Cancer site vs. electron beam energy indicated in IOERT procedures.

diagnosis. The type of surgery performed involves radical resection in a vast majority of cases.

After analysing the data distributed in 5-year periods, the results show that during the first three periods covered from 1995 to 2009, the distribution of the tumours most frequently treated with IORT remained practically constant, while in the last 2 years the treatment of breast cancer was

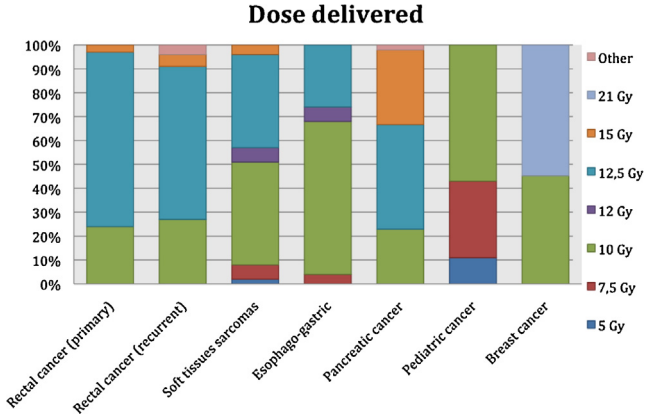

Fig. 4 – Dose delivered according to tumour site.

Table 1 – IORT technical parameters for all tumour sites.

	Rectal cancer (primary) (%)	Rectal cancer (recurrent) (%)	Soft tissues sarcomas (%)	Esophago-gastric (%)	Pancreatic cancer (%)	Paediatric cancer (%)	Breast cancer (%)
Applicator diameters							
5 cm	26	30	7	5	–	63	90
6 cm	37	20	6	11	6	11	10
7 cm	30	16	10	28	21	21	–
8 cm	6	16	11	43	51	5	–
9 cm	–	3	11	9	16	–	–
10 cm	–	9	22	4	6	–	–
12 cm	–	3	22	–	–	–	–
15 cm	–	3	11	–	–	–	–
Other	1	–	–	–	–	–	–
Electron beam energy							
4 MeV	–	–	3	–	–	16	–
6 MeV	1	16	37	37	18	42	74
8 MeV	5	11	24	30	33	11	4
10 MeV	19	16	11	12	15	5	6
12 MeV	35	24	13	16	8	16	16
15 MeV	33	20	7	–	8	10	–
18 MeV	7	13	5	–	18	–	–
Other	–	–	–	5	–	–	–
Dose delivered							
5 Gy	–	–	2	–	–	11	–
7.5 Gy	–	–	6	4	–	32	–
10 Gy	24	27	43	64	22	57	42
12 Gy	–	–	6	6	–	–	–
12.5 Gy	73	64	39	26	42	–	–
15 Gy	3	5	4	–	30	–	–
18 Gy	–	–	–	–	2	–	–
21 Gy	–	–	–	–	–	–	58
Other	–	4	–	–	4	–	–

introduced replacing esophago-gastric tumours as the third most frequently treated type with this technique. This fact also entailed a change in gender distribution.

Rectal cancer is, according to the data, the most frequent tumour site treated with IORT. This fact remains constant along all the extension of the survey. The IORT in rectal cancer aims to improve local control in locally advanced high-risk disease and in recurrent tumours where pelvic recurrence is responsible for therapeutic failure. Numerous literature studies showed a favourable local effect of IORT with high rates of local control in advanced primary cases and in recurrent tumours[4–8] but the only randomized trial conducted in 142 patients comparing conventional preoperative external radiotherapy (40 Gy) and with the same treatment plus IORT (15–18 Gy) failed to show an advantage for the experimental arm.[9] A recent meta-analysis extensively reviews IOERT studies in rectal cancer with a positive interpretation of results.[10] A distinction was made between primary rectal cancers and local recurrences. Data show that whereas primary disease had an exclusively curative treatment intention and a radical resection was achieved in almost every case, in local recurrences surgical residue was left in 16% of the cases and palliative treatment intention was performed in 11%. Treatment technical parameters are quite similar in terms of dose

Table 2 – Clinical and therapeutic correlations of surgical performance and technical IOERT characteristics according to cancer site.

	Rectum (primary) (%)	Rectum (recurrent) (%)	Soft tissues (%)	Esophago-gastric (%)	Pancreas (%)	Paediatric (%)	Breast (%)
Primary	100	0	61	96	96	65	100
Recurrent	0	100	39	4	4	35	0
Curative	100	89	98	100	87	90	100
Palliative	0	11	2	0	13	10	0
Radical resection	98	84	84	98	56	90	100
Surgical residue	2	16	16	2	32	10	0
No resection	0	0	0	0	12	0	0
Single field	98	89	80	77	100	89	100
Multiple field	2	11	20	23	0	11	0

and energy, whereas smaller applicators were required in primary disease. Also the need for multiple fields was higher in the treatment of local recurrences.

IORT is an anticipated radiation boost option in the multimodality treatment of soft-tissue sarcoma, especially because it enables the application of dose-dense irradiation to the target volume, or makes possible a lower EBRT target dose with corresponding inferior dose to surrounding healthy tissues. Sarcomas are the second most treated tumours, maintaining a constant percentage of cases during the 5-year periods evaluated. The intent of the treatments was almost exclusively curative with a high rate of radical resection. In terms of technical aspects, soft tissue sarcoma required a wide range of applicator diameters, most likely in relation with the heterogeneous tumour extension and post-resection tumour bed. Moreover, some cases required complex irradiations with multiple fields, with high energy electrons up to 18 MeV and doses up to 15 Gy.

IORT has potential utility in the treatment of oesophageal and gastric malignancies, in which the radiation tolerance of normal organs limits the dose that can be given with conventional radiotherapy techniques. Treatment of gastric cancer has a local failure in 50–70% of patients, mainly in those where an optimal surgery is not achieved. Therefore, radiation therapy has been shown to decrease local recurrence. After a number of studies,[11–13] it is possible to conclude that IORT is a treatment option with contradictory evidence, although it looks like its inclusion in the treatment of stomach cancer can decrease loco-regional recurrence, it does not appear to have an impact on overall survival. Similarly, it does not seem to cause an increase in morbidity or mortality. Our group has recently reported favourable results both in gastric and in gastro-oesophageal cancer treated with IORT-containing multimodal therapy.[14,15] According to the data, all treatments were performed with a curative intention and the surgery involved radical resection almost exclusively. The dose delivered was up to 12.5 Gy with relatively low predominating energies. The diameter of the applicators ranged from 5 to 10 cm and the highest rates in the application of multiple fields were obtained.

Pancreatic cancer is still one of the most lethal malignancies with an overall survival of less than 5% at 5 years. Only 20–40% of cases are operable, and even when a radical resection with negative margins is obtained, 5-year survival does not exceed 30%, with half of the surviving patients going to have a local recurrence over the next 5 years despite the use of preoperative or postoperative EBRT. Therefore, IORT could be an interesting therapeutic approach for this disease for dose intensification to improve local control in locally advanced cases. The potential of IORT in selected pancreatic cancer was widely reported by international experts.[16,17] Pancreatic cancer, according to the results, is almost the only cancer type, followed by a single case of cervix cancer that received IORT after a non-resective surgery and the third in frequency to be left with macroscopic or microscopic residue after surgical intervention. Despite this data, the treatments were performed with curative intent in the majority of cases. From the technical point of view, quite large diameters of applicators, i.e. up to 10 cm, were used with a large range of beam energy and dose levels most likely depending on the presence or removal of the pancreas and possible lymph node involvement, respectively.

Outcomes in paediatric tumours have improved considerably in the last decades. 80% of all children currently diagnosed are expected to be long-term survivors in almost every disease site and histology due to advancements in combined modality therapies. Because of dose-limiting organs in the abdomen and pelvis, adequate local control with acceptable treatment morbidity remains a problem in the treatment on these locations. This is the reason why IORT is an attractive treatment option for these locations. Other possible situations for the use of IORT in paediatric malignancies include those in which surgery and/or chemotherapy would not be expected to result in local control or in which EBRT doses in excess of 50 Gy would be necessary. In addition, there are cases in which the substitution of IORT for a part of the EBRT dose would decrease the dose to normal structures, and, therefore, minimize damage in these tissues. Data conclude that radical resection was achieved in all curative treatments. Technical parameters reveal the use of doses up to 10 Gy with a high range of energies, predominantly low energies as 6 MeV. The applicator size was variable but 5 cm applicators were used in more than half of the cases.[18]

In the last decades, clinical indications to IORT treatment have evolved significantly and expert centres incorporated this technique to the treatment of breast cancer. As the results show, the incorporation of breast cancer in this treatment modality is relatively late, but in the last 2 years the number of treatments performed became the third in terms of frequency. This fact might be related to a number of factors including the increasingly higher incidence of breast cancer and the launch of large clinical trials exploring IORT as a single radiation modality in an effort to shorten the overall treatment time of loco-regional therapy of breast cancer, and its implications.[19,20] The evidence of the efficacy of a single fraction of IORT, that represents a partial breast irradiation (PBI) strategy, is emerging in the last few years in particular for selected groups of patients.[21–23] In this regard, ESTRO and ASTRO recently formulated quite similar general criteria for the recommendation of PBI based on age, tumour stage, histology and hormonal receptor status. More than half of the patients of this survey were treated with this single radiation modality using a dose of 21 Gy. In patients who do not fulfil these criteria, the approach as anticipated boost is adopted as a current practice to boost the tumour bed, which was the strategy used in the other 42% of the patients. In expert IORT institutions, dose intensification has proven to result in outstanding low rates of local recurrence in already reported clinical studies.[24] The range of electron beams energy and collimator size (6 MeV and 5–6 cm being most frequently used) was most likely related to the tumour stage and to the size and shape of the breast but also to the extension of surgical incision for tumorectomy.

Recurrent pelvic disease and oligotopic intra-abdominal cancer are indications for surgical rescues that can be completed by IORT and external radiotherapy. Results along the last 20 years of publications are consistent with a potential for cure and acceptable tolerability.[25,8]

6. Conclusions

The data presented gives an overview on practice oriented patients selection, describes treatment modalities, analyses methodology and treatment related decisions for a number of tumour types which are treated and may benefit from this technique.[26,27] The opportunity to transfer radiosurgical expertise into technological developments (treatment planning system) is a remarkable feature that should be emphasized. Further data analysis will serve as a basis for designing clinical trials in an effort to define the contribution of IORT in tailored multimodality approach. Opportunities for prospective technological and biological research in IORT programmes have been recently reported.[14] Technological funded research in our group has covered much of treatment planning and dosimetry, image guided simulation, automation and pre-robotic IOERT, clinical practice normalization and self-training.

Conflict of interest statement

We declare no conflict of interest

Financial disclosure statement

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