

ISIORT pooled analysis 2013 update: clinical and technical characteristics of intraoperative radiotherapy

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Purpose: Data from centers active in intraoperative radiotherapy (IORT) were collected within the International Society of Intraoperative Radiation Therapy (ISIORT)-Europe program. The purpose of the present study was to analyze and report the main clinical and technical variables of IORT performed by the participating centers.

Materials and methods: Since 2007, ISIORT-Europe centers were invited to record data of IORT procedures in a common database. Other centers worldwide joined this initiative over time. Collected data included demographic, clinical and technical information.

Results: Thirty-one centers participated in the survey and data of 7,196 IORT procedures have been recorded to 2013. Median age of patients was 60.6 years (range, 5 months-94 years). Gender was female in 80.2% of cases and male in 19.8%. Treatment intent was curative in 7,054 cases (98%) and 1,587 patients (22.1%) were included in study protocols. The most frequent tumor was breast cancer with 5,654 cases (78.6%) followed by rectal cancer with 641 cases (8.9%), soft-tissue and bone sarcoma with 257 cases (3.6%), prostate cancer with 128 cases (1.8%), pancreatic cancer with 87 cases (1.2%), gastric cancer with 65 cases (0.9%), and esophageal cancer with 53 cases (0.7%). Treatment chronology shows how IORT number of recorded cases increased according with the interest in the ISIORT project.

Conclusions: This report gives an overview of patient selection and treatment modalities for the main tumor types effectively treated in a large group of active and experienced international centers using IORT. This data can be a basis for further surveys and for prospective studies devoted to analyze in depth IORT containing multimodal cancer treatment approaches.

Keywords: Intraoperative radiotherapy (IORT); International Society of Intraoperative Radiation Therapy (ISIORT) Europe; survey



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Introduction

Intraoperative radiotherapy (IORT) is a special technique allowing the delivery of a single high radiation dose during the surgical procedure. IORT evolved as an attempt to improve the therapeutic ratio by achieving intensification of radiation dose while limiting irradiation of healthy structures which can be surgically displaced (1-3).

IORT can be combined with external beam radiation therapy (EBRT) or used as a single radiation dose to provide the best combination of loco-regional treatment. The first treatment of IORT was reported by Comas and Prio in 1905 in a case of endometrial cancer (4). Subsequently, other applications were described for other tumor locations, including abdomen, chest and head and

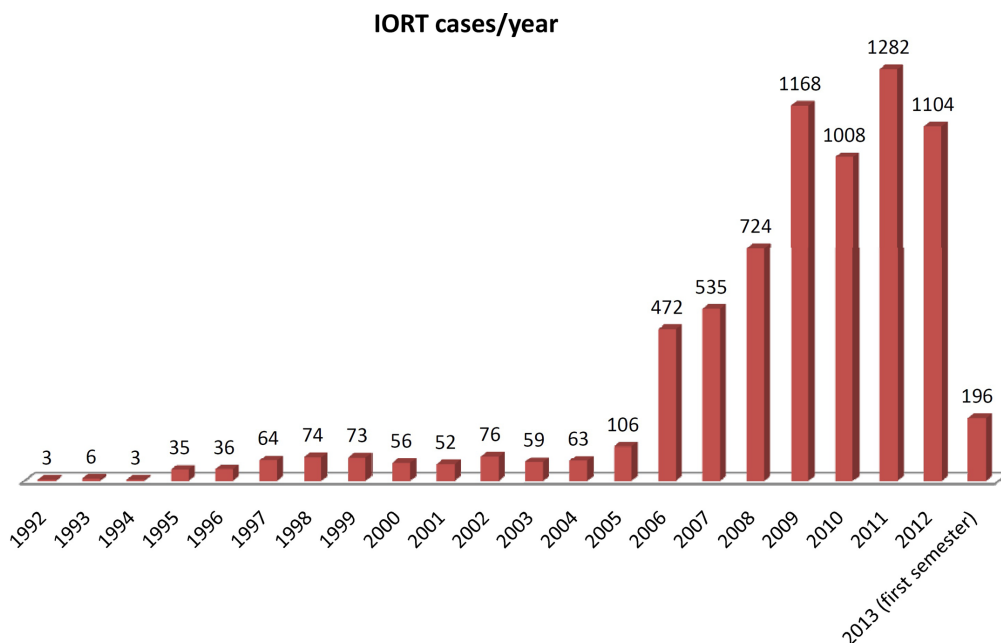


Figure 1 Chronological distribution of cases recorded in the ISIORT registry.

neck by using low energy X-rays (5) and, in the 60ies, by using single high doses of gamma-rays of cobalt units and electrons of betatrons (6). The scenario changed in the early 90ies when dedicated mobile electron linear accelerators and a miniaturized low-energy X-rays machine were introduced into clinical practice. Looking at the articles published in those years, most papers on IORT focused on single institution series or retrospective reviews (7). More recently, retrospective series, large pooled analyses and also randomized trials were published with an increasing interest in integration of IORT into treatment of early-stage cancers, in particular breast cancer for boost or partial breast irradiation (PBI) settings.

In order to promote a scientific and professional approach to IORT activity, the International Society of Intraoperative Radiation Therapy (ISIORT) was founded in 1998 and the European section of ISIORT (ISIORT-Europe) was activated in 2006.

We recently published the first report on a data-base registry of the ISIORT-Europe with focus on clinical and technical aspects of IORT, in predominant tumor sites (8). This is an update including 2012/2013 data and 11 new centers.

Material and methods

Since 2007, the ISIORT-Europe centers were invited to

record information of IORT treatments using the data-base registry. Real-time or retrospective data entry was allowed. Patient information was anonymized and integrated in a common data-base including demographic, clinical and technical information, tumor characteristic [such as staging according to TNM classification (9), treatment data, and specific IORT and EBRT data]. A detailed description of the data-base organization was published previously (8).

Results

Thirty-one centers contributed to this survey recording data of 7,196 IORT procedures performed from 1992 to 2013. The number of centers increased from 3 in 2007, when the initiative was launched, to 21 in 2011 and to 31 most recently. The average number of patients treated per year in each center was 42 and exceeded 100 patients/year in 4 centers. The chronology of cumulative activity is described in *Figure 1*. Median age of patients was 60.6 years with range of 5 months-94 years. Gender was female in 80.2% of cases and male in 19.8%. Median performance status on Karnofsky scale was 90% with a range of 40-100%. Tumor types are reported in *Table 1*. Treatments were applied with megavoltage electron linear accelerators in 6,863 cases (95.4%) and with kilovoltage device in 333 cases (4.6%).

Treatments intent was curative in 7,054 cases (98%) and

Table 1 Tumor sites/histologies treated with intraoperative radiation therapy (IORT)

Tumor site	Number of IORT procedures	%
Breast	5,659	78.70
Rectum	643	8.90
Soft tissue sarcoma	262	3.60
Prostate	128	1.80
Pancreas	87	1.20
Stomach	65	0.90
Esophagus	53	0.70
Uterine cervix	46	0.60
Brain	34	0.40
Head and neck	28	0.40
Ovary	16	0.20
Biliary tract	12	0.20
Colon	10	0.10
Lung	10	0.10
Kidney	8	0.10
Bladder	8	0.10
Sacrum	6	0.01
Adrenal glands	5	0.01
Other or undefined sites	116	1.60

palliative in 142 cases (1.9%). One thousand five hundred and eighty seven cases (22.1%) were included in study protocols. Data from the seven most frequent tumor types are specifically analyzed and reported in details.

Breast cancer

Data from 5,659 women with breast cancer were collected (Table 2). In 5,329 cases (94.1%), IORT was a component of radical treatment for primary newly diagnosed disease and in 330 cases (5.8%) it was an attempt to rescue localized recurrent breast cancer. In 52.2% of all indications, IORT was used as single radiation treatment modality with doses of 18 Gy (5%), 20 Gy (14.6%) or 21 Gy (80.4%) and in 47.8% as a boost before or after EBRT with doses of 8-12 Gy with electrons and from 8 to 20 Gy with low-energy X-rays. IORT was delivered before tumor removal in 37% of cases and after tumor removal in 63%. In case of recurrent tumor, 99% of IORT treatments were given as an exclusive radiotherapy component without EBRT. Patients enrolled in study protocols accounted for 20.2% of

the whole series, mainly deriving from single-dose IORT trials (33.0% of all respectively treated patients) and only to a lesser extent from boost trials (6.3% of all boost-IORT patients). In 248 cases (5%), IORT was performed with a 50 kV energy X-rays source. In these cases, a single shot of 20 Gy was the most frequently used modality (92.5%). In 218 cases (87.9%), the treatment intent was curative. All these cases were included in a study protocol. As to clinical setting we did not observe apparent differences between the cohorts treated by electron and X-rays sources. Technical characteristics of treatments are described in Figure 2.

Rectal cancer

Six hundred and forty-three patients with rectal cancer were treated with IORT (Table 2). In 553 cases (86.0%), IORT was used for primary disease and in 90 cases (16.3%) for isolated local recurrence. In 81% of cases, IORT was part of a multidisciplinary approach including EBRT, chemotherapy and surgery. In 92.3% of cases, the surgeon obtained R0 resection. In 97% of cases, IORT was delivered after tumor removal. Some information about technical aspects: most used applicator was 6 cm diameter (33%), followed by 5 cm in 28% of cases; in 83% of cases bevel angle was 45°. Median dose to tumor bed was 10.8 Gy (range: 5-21.6 Gy), 33% of cases received 12.5 Gy and 27% of patients received 10 Gy with 12 MeV (33%) or 15 MeV (30%) beam energies, respectively. In 18 cases (3.9%), IORT was delivered by a 50 kV energy X-rays source, with spherical applicators of 3.5-5 cm in diameter, to total surface doses between 6 and 21.6 Gy with the majority of cases in palliative treatment intent (61.1%). In 4 cases (22.2%), IORT was the unique radiation modality.

Sarcoma

Data from 262 cases of sarcoma were available (Table 2). In 54.6% of cases, IORT was used for primary tumor and in 45.4% for local recurrence. In primary tumor setting, radical tumor excision was achieved in 84% of cases. A multimodal treatment comprising EBRT, IORT, chemotherapy, and surgery was performed in 19% of the cases. IORT was delivered after surgical resection in 99% of cases. A single field was used in 74% of cases, multiple fields in 15%, a field-within-field technique in 6% and adjacent fields in 5%. Large collimators with diameters of 12-15 cm were used in 26.5% of cases and small collimators in the range of 4-6 cm in 17.8% of cases. Bevel angle was 30° in 43% of cases and

Table 2 Main patient and treatment characteristics of the five most frequent tumor sites/histologies

	Breast (n=5,659)	Rectum (n=643)	Soft tissue/bone (n=262)	Prostate (n=128)	Pancreas (n=87)
Centers	100%	45.1%	35.5%	16.1%	29.0%
Median age	61.1 years	62.9 years	50.0 years	67.5 years	64.5 years
Range age	16-90 years	26-94 years	2-88 years	51-86 years	34-82 years
Gender	M: 0% F: 100%	M: 63.4% F: 36.6%	M: 51.1% F: 48.9%	M: 100% F: 0%	M: 58.6% F: 41.3%
Histology	DC: 96.5% LC: 3.5%	ACA: 98.9% Other: 1.1%	Liposarcoma: 23.6% Fibrohistiocytoma: 8.0% Leiomyosarcoma: 7.9% Ewing sarcoma: 7.1% Synovial sarcoma: 7.1% Rhabdomyosarcoma: 4.1% Unspecified: 42.2%	ACA: 96.8% Sarcoma or other: 3.2%	ACA: 100%
Stage	Tis: 1.8% T1: 81.8% T2: 16.1% T3: 0.3%	T1: 12.9% T2: 57.1% T3: 16.4% T4: 13.6%	T1: 13.0% T2: 57.0% T3: 17.0% T4: 13.0%	T2a: 12.0% T2b: 7.8% T2c: 26.0% T3a: 42.5% T3b: 7.8% T4: 3.9%	T1: 9.2% T2: 43.6% T3: 26.8% T4: 20.4%
Single shoot	52.2%	51.6%	51.5%	52.3%	58.2%
Boost	47.8%	48.4%	48.5%	47.7%	42.8%
Curative/palliative	99.92%/0.08%	88.2%/11.8%	88.4%/11.6%	100%/0%	66.3%/33.7%
Prospective study	All: 19.4% Single shoot: 33.0% Boost: 6.3%	0%	0%	72.6%	0%

M, males; F, females; DC, ductal carcinoma; LC, lobular carcinoma; ACA, adenocarcinoma.

15° in 26% of cases. Median dose amounted to 11.5 Gy (range, 5-25 Gy) and the most frequently administered doses were 10 Gy in 44% of the cases and 12.5 Gy in 36% of the cases. Radiation beam energies ranged from 6 to 12 MeV. In 35 cases (13.4%), IORT was delivered with 50 kV X-rays with spherical applicators of 2.5-5 cm in diameter: 24 cases (68.6%) were recurrent tumors and the treatment intent was curative 29 cases (82.9%). Administered dose by X-rays was in the range of 5-20 Gy and in 20 cases (57.1%) the treatment was completed with EBRT.

Prostate cancer

One hundred twenty-eight patients with prostate cancer were treated with IORT in 5 centers (16.1%) (Table 2). All but 7 cases (94.5%) were primary, previously untreated tumors. IORT was used as a boost with doses of 8-15 Gy

and as a single radiation modality with doses of 18-21 Gy. In 74.2% of cases, IORT was delivered prior to prostate removal. Diameters of applicator were between 4 and 6 cm. In 80% of cases, 30° bevel angles were used. The mostly used radiation beam energies were 9 MeV (43%) and 12 MeV (40%). In 6 cases (4.7%), IORT was delivered with a 50 kV X-rays source with spherical applicators of 5.6-8 cm in diameter. All these patients had recurrent tumors and the intent of treatment was palliative. In these cases, doses of 5-8 Gy in a single shot were administered.

Pancreatic cancer

Data from 87 patients treated with IORT in 9 centers (29%) for pancreatic cancer were available (Table 2). Three cases (3.7%) were recurrent tumors. In 22.8% of cases, IORT was applied to unresected tumors and in 73.6% of cases after

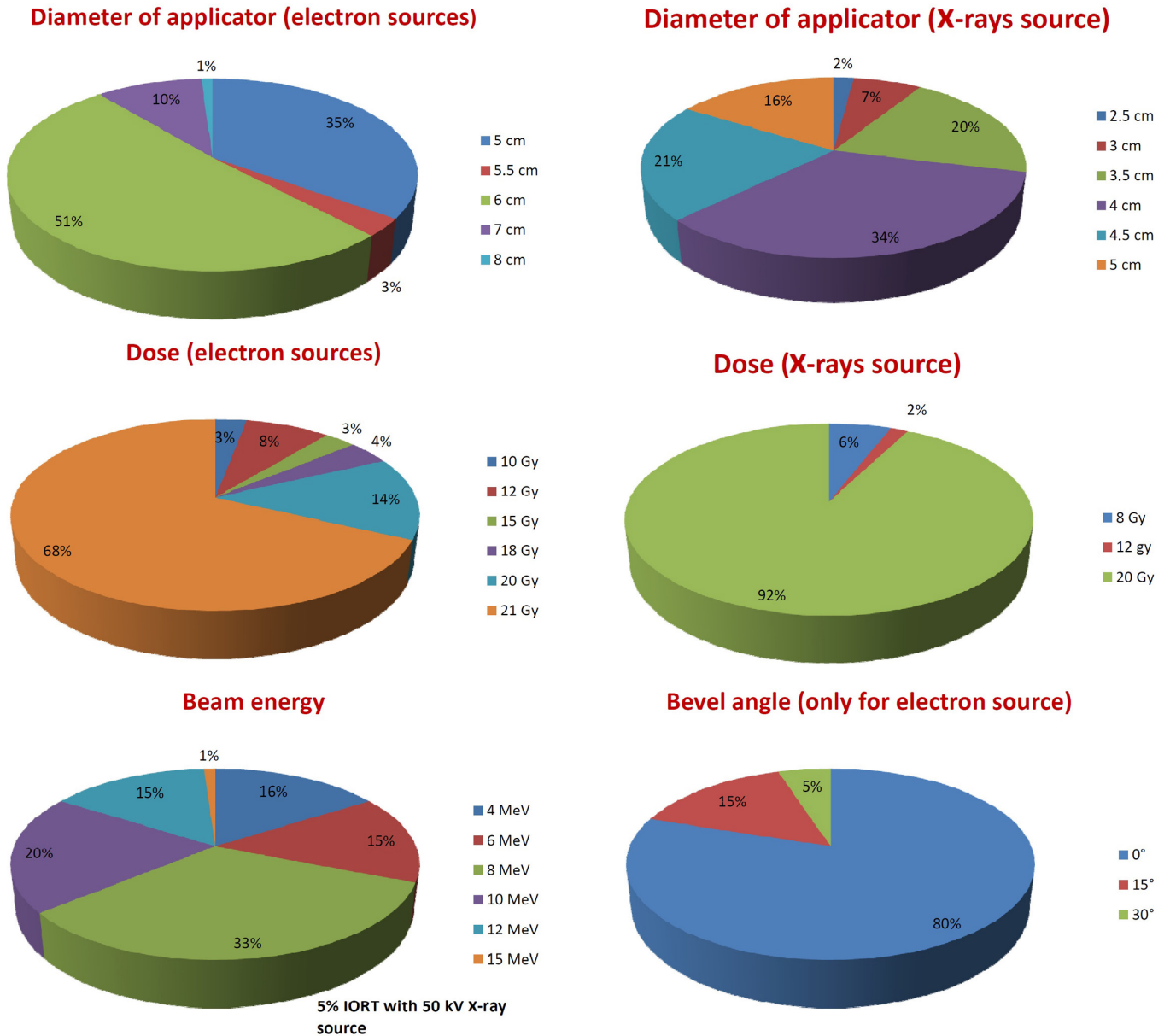


Figure 2 Breast cancer and main IORT technical characteristics of cases treated by electrons and 50 kV X-rays.

pancreatectomy. The median dose delivered was 13.6 Gy (7.5-21 Gy). Diameters of applicator were between 6 and 9 cm. In 48% of cases, bevel angles were 15° or 30°. Radiation beam energies were uniformly distributed between 8 and 18 MeV. All cases were treated with an electron source.

Gastric cancer

Sixty-five patients with gastric cancer (adenocarcinoma,

diffuse gastric cancer or gastric metastases) were treated with IORT in 4 centers (12.9%). Sixty-three patients were treated with curative intent, three of them (4.6%) affected by recurrent tumors, and two patients underwent surgery in palliative setting. In 59/65 cases (90.8%), surgeons obtained a radical resection.

Diameters of collimators ranged from 3 to 10 cm (8 cm in 32% of cases) and bevel angles from 0° to 30°, with 8 MeV as the most frequently used beam energy (47.7%).

Administered doses were in the 7.5-15 Gy range and 15 Gy was the most used dose level. In two recurrent gastric tumors (3.1%), IORT was delivered with 50 kV X-rays with applicator of 5 cm in diameter and a single dose of 8 Gy.

Esophageal cancer

Two centers (6.6%) sent data about IORT in esophageal cancer comprising 51 primary and two recurrent tumors (adenocarcinoma or squamous cell carcinoma). In all cases, intraoperative irradiation was part of a multidisciplinary approach including EBRT, chemotherapy and surgery. In 15/51 patients (29.4%), surgery with IORT followed pre-operative EBRT. The administered dose was in the 7.5-15 Gy range with an energy between 6 and 12 MeV. All these cases were treated with electrons.

Discussion

This survey collected 7,196 IORT data from 31 worldwide institutions updating the results of a previous study on 3,754 treatments from 20 institutions (8). The increasing number of collaborating centers over time reflects a rising interest in this initiative.

The vast majority of treatments were performed with megavoltage electron linear accelerators (95.4%), and only a minority of 4.6% with orthovoltage devices.

The database shows that all contributing centers treated breast cancer with IORT. For patients with early-stage breast cancer, adjuvant breast cancer treatment using IORT offers the advantage of reducing overall treatment time and improving quality of patients' life, as shown with the launch of large clinical trials exploring IORT (10-12), thus also reducing waiting lists in radiotherapy centers. Hence, increasing number of centers incorporate IORT in the multimodality treatment of breast cancer. The rationale of this treatment approach relies to the finding of about 85% of (at least first) local recurrences in the tissue adjacent to the lumpectomy site within five years of treatment after conservative treatment (13,14), prompting the interest for PBI to prevent majority of relapses. The efficacy of PBI by single shot IORT has been investigated in selected groups of patients (3,12,15,16). Prospective evidence about the potential of IORT as PBI strategy is generated mainly in two different multicenter trials: TARGIT and ELIOT, respectively, where 5-year experience is now available (17,18). With increasing follow-up periods, these studies will clarify if IORT-PBI following lumpectomy could be

considered as a sole radiation option in selected patients with favorable prognostic factors as an alternative to postoperative EBRT.

In this regard, the European Society for Radiotherapy and Oncology (ESTRO) and the American Society for Radiation Oncology (ASTRO) formulated quite similar general criteria for the recommendation of PBI (19,20). However, only 33% of patients treated by a single radiation fraction were included in protocol studies, meaning that a large number of patients was treated considering high dose IORT as current clinical practice for selected patients with favorable prognostic features based on preliminary results of clinical trials: this issue is still matter of discussion in the scientific literature (21,22). The most frequently adopted dose level in our survey was 21 Gy as in the ELIOT trial (18). Single-fraction was also used as re-irradiation strategy after breast conserving for in-breast tumor in 5.8% of cases of our series.

IORT as a boost technique was used in 47.8% of the patients and mostly outside clinical trials meaning that the approach of anticipated boost is adopted as a current practice. In expert IORT institutions, dose intensification has proven to obtain outstandingly low rates of local recurrence in already reported clinical studies (23,24).

IORT in rectal cancer aims to improve local control in locally advanced high-risk disease and in recurrent tumors where pelvic relapse is responsible for therapeutic failure. Undisputedly, achievement of R0 resection is the most important prognostic factor in colorectal cancer for subsequent local control. In situations where the radial margin is close or on vessels that are not amenable to resection, the goal of IORT is to eradicate microscopic tumor cells remaining within a few millimeters of the final surgical margin, while at the same time avoiding radiation exposure to small bowel, ureters, and bladder. Most cases of our analysis presented with locally advanced stage and a non-negligible percentage of patients (16.3%) were treated for locally recurrent disease. In the large majority of cases, IORT was given with curative intent as boost intensification dose and was part of a multidisciplinary approach including surgery, EBRT, and chemotherapy.

Several literature studies showed a favorable local effect of IORT with high rates of local control in advanced primary and in recurrent rectal tumors (25-31). Unfortunately, at the moment, there is only one phase III randomized trial compared preoperative radiotherapy followed by surgery (standard arm) with surgery and IORT (experimental arm) in 142 patients with a clinically T3, T4

or N+ and M0 rectal cancer (32). This trial failed to show an advantage for the experimental arm. A collective effort in designing and enrolling patients in prospective clinical trials may generate evidence in tailoring the indication of IORT for rectal cancer (33). Technical parameters of our survey were adequate to treat the presacral space and were quite similar to those reported in the European pooled analysis (34). Further developments in rectal cancer include the integration of IORT presacral electron boost during laparoscopic radical surgery (35).

IORT is used in the multimodality treatment of sarcoma because it enables the application of high-dose radiation to target volume and makes possible a lower EBRT dose with corresponding inferior dose to surrounding healthy tissues. IORT could also better avoid radiation exposure to joint spaces in extremities sarcoma. There is a large amount of published work on the use of IORT, and also HDR-IORT, in combination with surgery with or without EBRT for the treatment of retroperitoneal soft-tissue sarcoma and in sarcoma localized in the trunk or in the extremities (36-40). However, these studies are heterogeneous because in all of them there were patients who received IORT alone, while others received IORT plus EBRT, with the latter pre- or postoperatively. Prescription points and modalities also vary between the studies. Similarly our analysis showed quite heterogeneous subtypes. Almost half of the patients had recurrent tumors. In terms of technical aspects, soft tissue sarcoma required a wide range of applicator diameters and bevel angles, most likely in relation with the frequently large tumor extension and the post-resection tumor bed in soft tissues. Moreover, many cases required complex irradiations with multiple fields, or field within a field with high energy electrons up to 18 MeV and doses up to 25 Gy. Similar treatment modalities were described in other literature reports (37-39,41).

The rationale for dose escalation with IORT for prostate cancer is based on the demonstration of dose-response relationship and on the low α/β value in the linear quadratic model, a concept increasingly investigated in hypofractionated EBRT (42,43). Italian authors reported data using IORT in combination with radical prostatectomy and regional lymph node dissection before or after the surgical procedure (44-47). A large part of these patients (72.6%) was included in prospective institutional study protocols. In most of the cases, IORT was used as a boost dose prior to prostate removal with doses of 8-15 Gy and as a single radiation modality with doses of 18-21 Gy for single shot IORT. In our survey, a dose of 18-21 Gy was adopted.

The diameter and the bevel angle end of applicators were chosen on the basis of the target dimension considering a margin of at least 5 mm around the prostate and the necessity to reach the target underneath the pubic arch by sparing the bladder.

IORT is a potentially advantageous therapeutic approach for dose intensification to improve local control in locally advanced pancreatic cancer that still represents one of the most lethal malignancies in males with an overall survival of less than 5% at five years. From literature, benefit of the addition of IORT in patients was described for localized disease in particular in two multicentre analyses (48,49).

The registry has collected patients with locally advanced stages (mainly T2-T4) of pancreatic tumors, treated in most of the cases with curative intent after tumor resection. Most of these cases received multimodality treatments (surgery, adjuvant EBRT, neoadjuvant/adjuvant chemotherapy, biological targeted therapy). Case selection corresponded quite well to that of other literature studies (49). From the technical point of view, quite large diameters of applicators were used with a large range of beam energies and dose levels, most likely depending on the respective need to irradiate the unresected pancreas or the surgical tumor bed plus/minus regional lymph nodes. Recent data has reported that, in the context of chemoradiation and resection, the addition of IOERT boost significantly improves loco-regional control (50).

Defining the optimal role of radiotherapy regimens in the treatment of locally advanced gastric and esophageal malignancies remains an elusive goal. Although surgery remains the mainstay of curative therapy for both esophageal and gastric malignancies, investigators have long noted a high risk of local and regional recurrence in these malignancies. In this context, IORT has been investigated since Abe's first experience (6).

Concerning gastric cancer, an increase in loco-regional control of 12-15% has been reported in patients with IORT compared with those who did not receive IORT. However, overall survival has not improved in these series and complication rates are significantly higher following the use of IORT, which should be weighed carefully against the potential benefits (7,51-53). These elements explain why in the present survey only few and highly specialized centers have treated gastric cancer with IORT. From the technical point of view, a large diameter collimator was needed in most of the cases for an adequate coverage of the surgical bed and lymphatic drainages.

As far as esophageal cancer is concerned, IORT can be

a convenient modality to treat the lymph nodal volume which is a critical issue in particular in lesions located at the organ's middle and lower third. According to several studies, 58-74% of patients undergoing esophagectomy for thoracic esophageal carcinoma were diagnosed histologically as having lymph nodes metastasis (54). Recently, a study was published about the role of IORT targeted to the abdominal lymph node area in patients with esophageal carcinoma. This study revealed that the survival rate was significantly higher in favor for the use of IORT, without perioperative complications solely attributable to intraoperative irradiation (55). Of note in the present survey, all patients were treated in the context of a multidisciplinary approach meaning that the IORT boost was considered as a potentially advantageous modality for local dose intensification. In this context, a contemporary single institution cohorts analysis has shown that IORT electron boost, in post-chemoradiation resected status of locally advanced esophageal and gastro-esophageal junction carcinoma, significantly improves loco-regional control but not survival (56).

Oligo-recurrent and oligometastatic cancer are new clinical entities in which intensive local therapy (including radiation containing strategies) have proven to induce long-term survivors not expected with more conventional or conservative approaches (57). Systematic reviews have identified outcome benefits for the use of IORT components in the rescue of locally recurrent rectal cancer (58). Long-term single institution data have confirmed the potential of IORT in oligometastatic extrapelvic cancer (59) and oligo-recurrent gynecological cancer models (60).

The data presented are an update of the first report on a large clinical experience on patients treated with IORT and gives an overview on practice oriented patients' selections. Moreover, this survey describes aspects of patients' selection, chronological activity, treatment strategies and technical modalities for a number of tumor types which are currently treated and may benefit from this technique. The increasing number of collaborating centers will allow performing further data analyses based on a larger number of treatments, which could represent a solid basis for future collaborative prospective trials by identification of clinical partners.

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