Electron Intra Operative Radiotherapy

CLINICAL VERSATILITY AND UPDATES RESULTS

Update – December 2013

F. Trinchero
**ELECTRON INTRAOPERATIVE RADIATION THERAPY (IOERT)**

### Sommario

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1. INTRODUCTION
Intraoperative Electron Radiation Therapy (IOERT) is a procedure studied in depth since 1960. Its benefits are well known. IOERT as a component of the therapeutic approach allows intensification of the total radiation dose without additional exposure of healthy tissues and improves dose-deposit homogeneity and precision. As a single-dose irradiation, a major advantage is that it can provide full-dose radiotherapy during the surgical session, solving the problem of difficult access to radiotherapy centers experienced by many patients post-surgery. As a boost, dose escalation permits a high level of dose to the tumor bed, minimizing complications due to elevated radiation to healthy tissues.

Modern IOERT is mainly carried out with electron beams (IOERT) produced by linear accelerators used for external beam irradiation (EBRT) or by specialized mobile electron accelerators; true high performance miniaturized linacs, self-shielded, lightweight and easily maneuvered. Thanks to modern technology it’s now possible to irradiate directly during surgery, effectively, fast and safely, with simple radiation safety procedures; moreover, mobile linacs can be used in different surgical suites, covering the whole activity of an entire surgical department. These systems do not replace conventional EBRT linacs, they are complementary, with huge clinical, operative, social and economic benefits. With less than two minutes of irradiation, the operating room workflow is not interrupted. At present IOERT in vivo dosimetry is available. Treatment Planning Systems, Monte Carlo algorithms, e-IGIORT (Image Guided IOERT), fully automatic systems, intraoperative imaging assessment…. technology is already prepared to these new challenges.

IOERT has been defined as a multidisciplinary procedure, an activity in which the surgeon, radiation oncologist, physicist, pathologist, therapist and OR Personnel are all involved. A review of the scientific literature, including publications, trials, protocols and new pathologies treated shows how interest in this procedure has grown. “Multidisciplinary” means connection between several disciplines, in which each professional retains their autonomy and methodology and specific objects. Science, knowledge and skills must interact with each other, to reach a common target; a stage of maximum integration between different criteria and contribution, that gives life to a new medical discipline, merging into a new
epistemological context. This is transdisciplinary; a modern approach, a new philosophy: Interventional Radiation Oncology (IRO).

Our wish, in this report, is to stimulate interest in IOERT, focusing on clinical advantages and benefits in operations, economics and social issues. We hope to provide a full review of IOERT results for disease sites currently treated while annexing IOERT literature, including an analysis of future possibilities.

2. OPERATIONAL AND CLINICAL ADVANTAGES

The publication “Clinical and technical characteristics of intraoperative radiotherapy, Analysis of the ISORT-Europe database” (76) refers about 3,754 patients treated in 21 centers from 1992 to 2011 for different pathologies. In the following table Krengli, Calvo, Sedlmayer et al. summarized treatment characteristics in relation to the tumor size.

<table>
<thead>
<tr>
<th></th>
<th>Breast (N=2395)</th>
<th>Rectum (N=598)</th>
<th>Soft tissue/bone (N=221)</th>
<th>Prostate (N=108)</th>
<th>Pancreas (N=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centres</td>
<td>100%</td>
<td>57.1%</td>
<td>38.1%</td>
<td>23.8%</td>
<td>38.1%</td>
</tr>
<tr>
<td>Median age</td>
<td>60.8 years</td>
<td>63.0 years</td>
<td>43.8 years</td>
<td>67.2 years</td>
<td>64.6 years</td>
</tr>
<tr>
<td>Range</td>
<td>16–89 years</td>
<td>26–94 years</td>
<td>2–88 years</td>
<td>51–83 years</td>
<td>34–78 years</td>
</tr>
<tr>
<td>Gender</td>
<td>M: 6%</td>
<td>M: 63.9%</td>
<td>M: 51%</td>
<td>M: 100%</td>
<td>M: 57.5%</td>
</tr>
<tr>
<td></td>
<td>F: 100%</td>
<td>F: 36.1%</td>
<td>F: 49%</td>
<td>F: 0%</td>
<td>F: 42.5%</td>
</tr>
<tr>
<td>Histology</td>
<td>DC: 96.3%</td>
<td>ACA: 98.7%</td>
<td>Liposarcoma: 23.5%</td>
<td>ACA: 100%</td>
<td>ACA: 100%</td>
</tr>
<tr>
<td></td>
<td>LC: 3.7%</td>
<td>Other: 1.3%</td>
<td>Fibrohistiocyoma: 8.1%</td>
<td>(with neuroendocrine component in 6.2%)</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td>Tis: 1.6%</td>
<td>T1: 3.7%</td>
<td>T1: 13.0%</td>
<td>T2a: 12.0%</td>
<td>T1: 6.5%</td>
</tr>
<tr>
<td></td>
<td>T1a: 82.5%</td>
<td>T2: 11.1%</td>
<td>T2: 57.0%</td>
<td>T2b: 7.8%</td>
<td>T2: 35.5%</td>
</tr>
<tr>
<td></td>
<td>T2b: 15.7%</td>
<td>T3: 70.3%</td>
<td>T3: 17.0%</td>
<td>T3c: 26.0%</td>
<td>T3: 25.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T4: 15.0%</td>
<td>T4: 13.0%</td>
<td>T3a: 42.8%</td>
<td>T4: 19.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T3b: 7.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T4: 3.9%</td>
<td></td>
</tr>
<tr>
<td>Boost</td>
<td>51.9%</td>
<td>16.2%</td>
<td>51.6%</td>
<td>52.3%</td>
<td>60.0%</td>
</tr>
<tr>
<td></td>
<td>48.1%</td>
<td>83.8%</td>
<td>48.4%</td>
<td>47.7%</td>
<td>40.0%</td>
</tr>
<tr>
<td>Curative</td>
<td>100%</td>
<td>95.0%</td>
<td>90.0%</td>
<td>100%</td>
<td>81.2%</td>
</tr>
<tr>
<td>Palliative</td>
<td>0%</td>
<td>5.0%</td>
<td>10.0%</td>
<td>0%</td>
<td>18.8%</td>
</tr>
<tr>
<td>Prospective study</td>
<td>All: 19.4%</td>
<td>Single-shot: 33.0%</td>
<td>Boost: 6.3%</td>
<td>80.6%</td>
<td>0%</td>
</tr>
</tbody>
</table>

An example of the use of IOERT is the conservative treatment of breast cancer in postmenopausal patients. After tumor removal, one sole application of IOERT (SINGLE DOSE) of 21 Gy (approximately one minute long) is carried out. A one minute treatment of IOERT delivered in the OR replaces six weeks of standard EBRT post-surgery. If it’s true that the “single dose” is a stunning treatment, thanks to e-IORT BOOST, equally true and important is the possibility to reach high total doses with the “dose escalation” model. For some type of patients it would be necessary, for local control of the disease, to deliver doses of external beam radiation exceeding 60 Gy divided in 1.8-2 Gy per day. But this value is impractical: doses higher than
45-50 Gy cannot be administered due to its toxicity in healthy organs. Only with a boost at the time of surgery can we reach high dose value, because biological effects of an intraoperative radiotherapy irradiation are 2-2.5 times more than the same dose value in EBRT (1). This means that with a 10 Gy boost of IOERT followed by 45-50 Gy EBRT, we can administer an effective dose of 70-75 Gy. With an IOERT boost of 15 Gy an effective dose of 82-87 Gy and 95-100 Gy with an IOERT boost of 20 Gy. Reduction of the waiting list on conventional accelerators not only allows improved workflow but has an important effect on operational and efficiency of a radiotherapy department. By reduction of the fractionation schedule for breast cancer, more time slots are available for treatment of other EBRT patients, helping to eliminate waiting lists. Studies have shown that radiation therapy is most effective when delivered at the time of tumor excision (“zero time”). In addition, tumor targeting, dose homogeneity and protection of the heart and lungs is assured. Chemotherapy is able to be started earlier. Local recurrences are conditioned by the time between surgery and radiotherapy and calculated their increase of 1.1% for every month of delay. Huang found 16% of local recurrence in chemotherapy followed by radiotherapy and 6% in the radiotherapy followed by chemotherapy; moreover the local recurrence rate appeared to double if EBRT was started after 8 weeks post surgery. Experimental studies on animals showed that radiotherapy at “zero time” has the maximum effectiveness. Randomized studies showed that adjuvant radiotherapy, started immediately after the operation, reduces development of subsequent development metastasis.
3. SOCIAL BENEFITS AND PATIENT COMFORT
Fewer irradiation sessions, less traveling to Radiation Oncology departments, less discomfort... with the use of single dose in operating room with IOERT, social and economic benefits have not yet been quantified, but they are obvious. Emotional involvement of the patient that waits, sometimes long months, for the first session in radiotherapy, the discomfort in moving the patient (often accompanied by relatives, kilometers away, car and fuel expenses, traffic and pollution), the stress of the radiotherapy session, in environments that are not very comfortable are particularly challenging. Arguments are many, while not easily quantifiable, are definitely noticeable and significant in terms of quality of life. Athas study, (2) in the USA, showed that there is a relationship between problems of reaching radiotherapy facilities and the number of mastectomies performed. Breast conservation was chosen 82% of the time if the radiotherapy facility was less than 10 miles away, 69% with a distance between 50 and 75 miles and 42% for distances greater than 100 miles. Moreover, with large and prolonged waiting lists, women do not receive optimal treatment; long delays in beginning radiotherapy (which standard protocols state should not exceed 40 days after the operation) reduce its effectiveness. Chen (3) calculates that there is an increase of 1.1% in the absolute risk of local recurrence for every month of delay.

4. ECONOMIC BENEFITS
Aforementioned social benefits also result in economic added values that can be easily understood. Taking into account of the prestige that brings IOERT availability in local territory with a strong appeal to patients, a mobile Linac for IOERT installed in a radiotherapy department results in a significant return on investment. Compared with a turn-key fixed Linac installations, purchase cost of an IOERT system is reduced by more than 70%. Detailed ongoing studies comparing activity with a conventional Linac systems vs IOERT (4) (5) show that the single dose IOERT availability saves 52% of the total management cost. It should also be noted that:

Single dose breast irradiation permits radiation oncology departments to focus their activity on more complex and economically favorable irradiation procedures
Time of staff involved in an e-IORTIOERT session lasts 10-15 minutes vs 30-40 total minutes in EBRT
Number of personnel involved in e-IORTIOERT is just two-three people with very low activity for the preparation of radiation treatment plans
Thermoplastics material for external irradiation is not needed IOERT
Maintenance costs are also reduced by a significant percentage

5. CLINICAL RESULTS

5.1. BREAST CANCER
As reported in an analysis of the ISIORT Europe database (76), clinical indications for IORT treatment have evolved significantly and expert centers have incorporated this technique into breast cancer therapy. In this study IOERT was performed using electrons in 92% of patients, treated in 20 centers.

5.1.1. BOOST
Considering the tumor bed as the tissue at highest contamination with subclinical tumor cells, a local dose escalation has proven to lower in-breast recurrence rates most effectively. More, direct exposure of the tumor bed may eliminate the possible inaccuracy of location allowing treatment of a more limited volume of glandular tissue.
Results with patients with invasive breast cancer had been published. (15) Patients had been treated to the whole breast (51–56.1 Gy in 1.7 Gy fraction) either with conventional external beam electron boost in group 1 (fractionated dose of 12 Gy) or with IOERT boost in group 2 (single dose of 9 Gy). With a different median follow-up period (55.3 months in group 1 and 25.8 months in group 2), the results of this sequential study showed that IOERT boost yielded excellent LC (local recurrence rate of 4.3% in group 1 and 0.0% in group 2) and appears to be superior to the conventional postoperative boost.

Sedlmayer (16) defined “The Salzburg Concept of IOERT”: the aim is not to reduce radiation times, but to reduce local recurrences. Authors report a prospective study regarding two groups of similar patients (table 2). All 190 patients of the second group had negative margins. Collimators used were 5-6 cm, therefore 3 cm of healthy tissue were irradiated compared with the extension of the later diseased foci. Time between IOERT and external radiotherapy of the patients who underwent radiotherapy was 20 weeks. The Salzburg group (IOERT 2008) also refers to a pooled analysis of 1,200 patients coming from different centers treated with the same Salzburg methods and with an average follow-up of 59.6 months. Local recurrences 0.5%, collimators used 5-8 cm.

<table>
<thead>
<tr>
<th>GROUP 1 (EBRT)</th>
<th>GROUP 2 (e-IORT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Breast Tumor Recurrence</td>
<td>4.3%</td>
</tr>
<tr>
<td>Distant recurrences</td>
<td>8.6%</td>
</tr>
<tr>
<td>Survival</td>
<td>90.9%</td>
</tr>
</tbody>
</table>

Table 2: the concept of ioert according to the Salzburg group. Follow-up results after 5 years. GROUP 1 -188 patients total irradiation (30 x 1.7 G) 51 Gy + boost 16 Gy. GROUP 2 -190 patients IOERT (boost 9 Gy) + total irradiation (30 x 1.7 G) 51 Gy.

Since 2011 Sedlmayer’s et al. (17) HIOB protocol (Hypofractionated Whole-Breast Irradiation preceded by Intra-Operative Radiotherapy with Electrons as anticipated Boost) is ongoing in many hospital in Europe an USA. HIOB is defined as hypofractionated WBRT (40,5 Gy in 2,7 Gy per fraction) preceded by an Intra-Operative Boost, performed on mobile or fixed Linacs with variable electron energies between 4-12 MeV, to the tumor bed ( 90 % reference dose of 10 Gy, 11.1 Gy Dmax IOERT ). The HIOB study concept is supposed to test the hypothesis whether such a combined schedule is superior (or iso-effective) towards "standard" RT in terms of local control and cosmetic outcome.

Finally, in 2013, a pooled analysis done using ISIORT data (1.109 patients) shows great results in terms of LR; taking into account patient age, annual in-breast recurrence rates amounted 0.64%, 0.34%, 0.21% and 0.16% in patients <40 years; 40–49 years; 50–59 years and +60 years, respectively (75). IOERT seems to yield local control rates in every risk group which has not been shown before by any other method in trials with comparable size and follow-up. The effect was reproducible in every participating center. Interestingly, even long time delays between IOERT and WBI – mainly caused by adjuvant chemotherapy – did not compromise local control. In our analysis, we were able to demonstrate the validity of this concept in a long term follow up, suggesting boost-IOERT as a highly effective asset in the radio-oncologic portfolio.
5.1.2. SINGLE DOSE - ELIOT

In November 2013 European Institute of Oncology (IEO) in Milan (7) (8) (9) (10) (11) with Veronesi, Orecchia et al. published ELIOT trial (78) about the use of 21 Gy in the context of breast conserving surgery without EBRT complement in patients with tumor size below 2.5 cm. The rationale for the use of this segmental RT, explained in Bernier et al. (12) in place of whole-breast irradiation is based on the results of long term studies: for instance, the results at 12-year follow-up of the Milan III trial, which compared quadrantectomy alone versus the same conservative surgery plus EBRT on the whole breast, have confirmed that 85% of local relapses were in or close to the previous index quadrant (13) and the incidence of local relapses was found to be significantly lower in patients older than 55 years and equal in both arms in those older than 65 years.

With e-IORT it is possible to:

- reduce radiation field only to the involved quadrant of the breast
- change the course from 5 to 7 weeks to one single, intensive dose in the operating theatre immediately following surgical resection.
- minimize problems related to the external side effects since the skin and subcutaneous tissue are not irradiated and the spread of irradiation to lung and heart is significantly reduced.
- Irradiate tumor bed with an highly precise homogeneous dose distribution
- Manage easily depth of the tissue to be irradiated

All these advantages enable the target area to be irradiated with minimal margin of error. ELIOT technique may be used as a single treatment administering 21Gy in approximately 60-80 seconds.

(14)

- 2000-2008, 1,822 patients, IEO-Milan, T<2.5cm
- 21Gy alone, MFT 36 months
- 1.3% in-breast ipsilateral, 2.3% in-quadrant, 89 % OS @ 10-y

LC influenced by age, size-N, Cerb++, grade, perineural
**ELIOT TRIAL FINAL RESULTS**

The ELIOT Trial (78) considers that women aged 48–75 years with early breast cancer, a maximum tumour diameter of up to 2.5 cm, and suitable for breast-conserving surgery were randomly assigned in a 1:1 ratio (using a random permuted block design, stratified for clinical tumour size (<1.0 cm vs 1–0.1.4 cm vs ≥1.5 cm)) to receive either whole-breast external radiotherapy or intraoperative radiotherapy with electrons. Patients in the intraoperative radiotherapy group received one dose of 21 Gy to the tumour bed during surgery. Those in the external radiotherapy group received 50 Gy in 25 fractions of 2 Gy, followed by a boost of 10 Gy in five fractions. This was an equivalence trial; the prespecified equivalence margin was local recurrence of 7.5% in the intraoperative radiotherapy group. 1305 patients were randomised (654 to external radiotherapy and 651 to intraoperative radiotherapy) between Nov 20, 2000, and Dec 27, 2007.

After a medium follow-up of 5.8 years we found these results:

<table>
<thead>
<tr>
<th></th>
<th>External radiotherapy (n=654)</th>
<th>Intraoperative radiotherapy with electrons (n=651)</th>
<th>Log-rank p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>5-year event rate (95% CI)</td>
<td>Number</td>
</tr>
<tr>
<td>Ipsilateral breast tumour recurrence</td>
<td>4</td>
<td>0.4% (0.0-1.0)</td>
<td>35</td>
</tr>
<tr>
<td>Local relapse</td>
<td>4</td>
<td>0.4% (0.0-1.0)</td>
<td>21</td>
</tr>
<tr>
<td>New ipsilateral breast tumour</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
</tbody>
</table>

Overall Survival at 5 years did not differ between the two groups. As reported in David Azria, Claire Lemanski comments (79) The new data from ELIOT reinforce our conviction that intraoperative radiotherapy during breast-conserving surgery is a reliable alternative to conventional postoperative fractionated irradiation, but only in a carefully selected population at low risk of local recurrence.
5.2. COLORECTAL CANCER
As reported in the ISIORT database analysis in (76), of the registered patients, 598 with rectal cancer were treated using IORT. IORT was used for primary disease and isolated local recurrence in 514 (85.9%) and 84 (14.1%) cases, respectively. In 79% of cases, IORT was part of a multidisciplinary approach including EBRT, chemotherapy and surgery. In 91.9% of cases, the surgeon obtained R0 resection. In 97% of cases, IORT was delivered after tumor removal. IORT was performed by electrons in 98% of cases, treated in 12 centers.

5.2.1. PRIMARY LOCALLY ADVANCED CANCERS
Local control in rectal cancer patients is related to the dose of irradiation, but because of toxicity to radiosensitive organs included in the pelvic space such as small bowel, ureter and bladder, the external radiation dose should not exceed 60 Gy. In a 2007 publication De Wilt et al. (18) reported that a combination of external radiation and intraoperative radiation therapy (IOERT) allows the safe delivery of higher effective doses of irradiation than can be delivered with external-beam-only techniques. IOERT is used when resection margins are close or involved and can be applied very specifically to an area at risk, under direct visual control, and with the ability to shield the surrounding structures from radiation. The biological effectiveness of single-dose IOERT is considered to be as effective as 2 to 3 times the equivalent dose of fractionated radiotherapy. The advantages of IOERT are the treatment depth of > 1 cm with a choice of electron energies and quick delivery of the radiation. Several studies have reported that IOERT was feasible, safe, and improved both local control and overall survival. (19) (20) (21) (22) Because there is a good rationale for dose escalation in locally advanced cancer, IOERT is a promising technique for further improving local control and overall survival.

In a study on 99 patients Sadahiro et al. concluded that the combined preoperative radio/chemo-radiotherapy and IORT for clinical T3-4 Nx rectal cancer significantly reduces local recurrence and improves prognosis. (23) Combination of preoperative radiotherapy and oral tegafur and uracil improves the feasibility of sphincter-preservation.

The European pooled analysis of IORT (76) containing multimodality treatment for locally advanced rectal cancer in 605 patients showed a local recurrence rate of only 12% in a very high-risk group of patients.

5.2.2. LOCALLY RECURRENT CANCERS
Roeder, Debus et al. (24) study 97 patients between 1991 and 2006 with locally recurrent rectal cancer, treated with surgery and IOERT. IOERT was preceded or followed by external beam radiation therapy (EBRT) in 54 previously untreated patients (median dose 41.4 Gy) usually combined with 5-Fluouracil-based chemotherapy (89%). IOERT was delivered via cylindrical cones with doses of 10–20 Gy. Adjuvant CHT was given only in a minority of patients (34%). Median follow-up was 51 months. Multimodality treatment including surgery, IOERT and EBRT resulted in encouraging LC and long term OS in a substantial proportion of locally recurrent rectal cancer patients, especially if free margins could be achieved.

Data supporting the use of IOERT for locally recurrent disease and no evidence of extra pelvic spread was also found in Mayo Clinic analysis of 106 patients treated with palliative resection.

IOERT (mostly from 15 to 20 Gy) was given as a component of the treatment in 42 patients and EBRT in 41 (no more than 45 Gy). (25)
5.3. PANCREATIC CANCER

Pancreatic cancer is the 10th most commonly diagnosed cancer and the 4th leading cause of cancer death in the U.S. The survival rate for this deadly disease has not improved substantially in nearly the last 40 years even with aggressive treatment, because recurrence rate after cancer resection is high, due to persistence of microdisease. It remains one of the most lethal types of malignancy, with an overall 5-year survival rate of less than 5%. Several literature studies have described favorable effects of IORT in pancreatic cancer, but the results preclude clear interpretation since this technique was used in the context of multiple treatment strategies. For all stages combined, the 1 and 5-year relative survival rates are 25% and 6%, respectively. For patients diagnosed with local disease, the 5-year survival is only 22%. To eradicate microscopic disease it has been shown that administering 60 Gy fractioned in 1.8-2 Gy is necessary (26), but dose-sensitive structures close to tumor bed (stomach, transverse colon, bile duct…) limit use of radiation. IOERT is a partial answer, because it allows the administration of a single high dose of radiation during the surgical procedure targeted at the tumor bed to eliminate any microscopic remains of tumor with the advantage of being able to displace and shield healthy tissue.

Reni M. et al (27) indicated that for patients with pancreatic cancer stage I-II disease, IOERT reduced the local failure rate from 60% to 27%. They have reported the comparative outcome of 203 patients treated at the San Raffaele Hospital in Milan in the period 1985–1998 from which 127 had IOERT. IOERT did not increase operative morbidity or mortality and achieved a significant improvement in LC (60% versus 27%) and 6-year OS (24% versus 8%) in stage I and II. In more advanced stages (III–IV) the impact in LC was observed only if the electron beam energies were superior to 6 MeV. Alfieri et al noted increased local control with the addition of IOERT in resected pancreatic cancer and they found that local control was 58% in the IOERT group vs 29% in the group that not receive IOERT (28). Zerbi et al reported that local recurrence was detected in 27% of patients treated with surgery + IOERT and in 56% of patients treated with surgery alone. (29)

The combination of EBRT and IOERT has resulted in improved local control (LC) in separate series from MGH (30) and Mayo Clinic (31) (32). A remarkable contribution from MGH (33) is a publication in which eight long-term surviving patients (five of them more than 5 years) are identified among 150 treated with IOERT in the period 1978–2001 for unresectable but non-metastatic disease.

A retrospective analysis from Japan, 2012 ISIORT, (34) give results of intraoperative radiotherapy (IOERT) with or without external beam radiotherapy (± EBRT) for localized pancreatic cancer in the past three decades and to analyze prognostic factors by multivariate analysis. Records for a total of 322 patients with pancreatic cancer treated by IOERT ± EBRT were reviewed. Results report that there is an excellent local control for pancreatic cancer with few cases of severe late toxicity by using IOERT. OS of patients with pancreatic cancer treated by IOERT ± EBRT improved significantly decade by decade. Multivariate analysis showed that degree of resection and adjuvant chemotherapy had significant impacts on OS.
5.4. GASTRIC CANCER
Worldwide experience generated in the last 20 years has shown that IOERT is a feasible technique to be incorporated in gastric cancer surgery. IOERT seems to promote Local Control and Survival values superior to historical surgical controls (failures rates ranged from 10 to 44%). It is conventionally accepted that EBRT and chemotherapy further contributes to increase LC. Recommendations to integrate IOERT in the multimodal approach are based in clinical data with intermediate level of evidence (prospective phase II or retrospective studies). An IOERT component has been included in the context of neoadjuvant chemotherapy, surgical resection and EBRT with acceptable tolerance (35). Nevertheless, tendencies in treatment strategies for locally advanced gastric cancer are to maximize combined modality therapy and better identify subgroups of patients that might benefit from intense loco-regional treatment including an IOERT component (36) (37). High-risk gastric cancer seems to benefit from multimodality therapy as demonstrated by the recent report for Intergroup (38).

In 2007 University of Freiburg published a retrospective analysis with the impact of intraoperative radiation therapy (IOERT) alone, w/o external irradiation or chemotherapy, on long-term survival in patients with resectable gastric cancer. Use of IOERT was associated with low locoregional tumor recurrence, and while it had no benefit on long-term survival, it significantly decreased surgical morbidity in patients with curable gastric cancer (39).

Skoronad et al. (40) have recently reported a randomized trial comparing preoperative radiotherapy (20 Gy in 5 days), gastrectomy and IOERT (20 Gy) to surgery alone. No chemotherapy was used in the trial. Distribution of postoperative complications was similar in both groups. Survival in early stages was not influenced by treatment type. On the contrary, combined treatment has marked OS advantage in more advanced stages: N+ (42% versus 21%, p = 0.04) and pT3-4 (60% versus 15%, p = 0.04).

Intraoperative radiotherapy (IOERT) has been tested at the National Cancer Institute randomized trial; (41) 41 patients were treated with surgery (control arm: early stages) and postoperative radiotherapy (control arm: advanced stages), or with surgery and IOERT (experimental arm: all stages). Locoregional recurrence rates were lower for the IOERT group (44% versus 92%, P < 0.001), but this did not translate into a difference in survival. There were no differences in complication rates. A German study that randomized 115 patients for surgery or surgery plus IOERT (single dose 28 Gy) also did not show a significant difference in overall survival.

Based on these underpowered studies, adjuvant radiotherapy as single modality following surgery has no role in routine daily clinical practice. IOERT might be further investigated in patients with unfavorable tumor characteristics.
5.5. GYNAECOLOGIC CANCERS

In the 2006 comprehensive publication of Calvo, Orecchia et al. and in the re-edition of the textbook of Gundarsson too, it is reported that (6) in patients with locally recurrent gynaecologic cancer in the pelvic sidewalls and/or para-aortic or pelvic lymph nodes, the use of maximum effort salvage surgery (including extended resection), IOERT, with or without EBRT, and the combination of systemic therapies may be beneficial when compared with standard EBRT. The 5-year OS were 27 and 32% respectively in the separate series from Mayo Clinic (42) and the University of Washington (43). Patients with only microscopic residual disease after maximal resection at the time of IOERT had significantly higher 5-year OS rate than those with gross residual disease (37% versus 10%, p = 0.02). The risk of distant metastases at 3 years was 42% (77% with gross residual and 31% with microscopic residual, p = 0.001). There was a trend towards fewer metastases (27% at 5 years) in patients who received chemotherapy (p = 0.09). Based on the higher response rate observed in patients receiving chemotherapy and the observed trend toward improved distant control and DFS, Mayo Clinic is using systemic therapy before surgery and IOERT as standard treatment.

The University of Navarre in Pamplona has evaluated the incorporation of preoperative chemo radiation, surgery, and IOERT in the treatment of locally advanced primary cervical cancers (44) From 1988 to 1997, 40 patients (stages IB2-IVA) were treated with preoperative chemo-radiation (45 Gy plus Cisplatin 20 mg/m2 at weeks 1 and 5, with 5-FU 1500 mg days 1–4 and 22–25), followed by surgical resection in 4–6 weeks including an IOERT boost (10–15 Gy) to the parametrial resection margins and iliac nodal regions. Pathological CR rate at the time of surgery was 67%. There were only three local failures. Nine-year OS was 75%. Three patients developed postoperative uretro-vaginal fistula and 5 long-term hydronephrosis. Ten years in-field LC rates of 92 and 46%, respectively for primary and recurrent disease, have been reported. The LC rate was correlated with positive parametrial margins (p = 0.001) and pelvic lymphonode involvement (p = 0.032). Calvo, Sole et al. published in (77) that 35 patients with LRGC [uterine cervix (57%), endometrial (20%), ovarian (17%), vagina (6%)] underwent extended [multiorgan (54%), bone (9%), soft tissue (54%), vascular (14%)] surgery and intraoperative electron-beam radiation therapy [IOERT (10–15 Gy)] to the pelvic recurrence tumor bed. With a follow up of 46 months, ten-year rates for locoregional control (LRC) and overall survival (OS) were 58 and 16%, respectively, and that suggest that a significant group of patients may benefit from EBRT treatment integrated with extended surgery and IOERT.
5.6. RETROPERITONEAL AND PELVIC SOFT TISSUE SARCOMAS

The retroperitoneum can host a wide spectrum of neoplastic disease, including a variety of rare benign tumors and malignant neoplasms that can be either primary or metastatic lesions. Retroperitoneal tumors can cause a diagnostic dilemma and present several therapeutic challenges because of their rarity, relative late presentation and anatomical location, often in close relationship with several vital structures in the retroperitoneal space.

Radiotherapy improves local control in extremity sarcomas and has become standard practice. However, RPS presents several radiotherapeutic challenges. These tumors are often adjacent to radiosensitive structures with low radiation tolerance. Retroperitoneal sarcomas compose a heterogeneous group of pathologies with variable radiosensitivity. In an attempt to reduce the radiation toxicities, studies have evaluated the treatment planning with conformal therapies such as intensity-modulated radiation therapy or the use of intraoperative radiotherapy.

In the 2006 comprehensive publication of Calvo, Orecchia et al. it is reported that (6) IOERT combined with resection and EBRT offers an effective means of improving LC in patients with retroperitoneal sarcomas, as seen both in the randomized study from the NCI (45) and in other single-institution studies in the United States (46) (47) and Europe (48) (49). On the basis of the NCI randomized trial, however, the use of adjuvant EBRT without IOERT after marginal resection could be questioned because the same rate (80%) of tumor bed relapse has been observed in both the arms of adjuvant EBRT and surgery alone.

A more practical approach is to give preoperative EBRT (with or without concomitant chemotherapy) after thin-needle biopsy and perform the resection at an institution that has the capability of giving an IOERT supplement. However, the incidence of local, regional, and distant failures is still frequent, emphasizing the need for further improvement in local therapy and effective systemic treatment. Pilot studies are being developed to combine maintenance with or without concomitant chemotherapy with EBRT and IOERT for moderate and high-grade retroperitoneal and pelvic sarcomas, both primary and locally recurrent. Pisters et al. (50), at MD Anderson, have reported a phase I trial using preoperative concurrent doxorubicin and EBRT (escalating doses from 18 to 50.4 Gy), followed by surgical resection and IOERT. Twenty-nine of 35 patients underwent laparotomy (R0 or R1 resection achieved in 90%) and IOERT was delivered to 22 patients. The dose of 50.4 Gy was reached in 11 patients (2 had grade 3–4 nausea).
5.7. EXTREMITY SARCOMAS

Prior to the introduction of radiotherapy for extremity soft tissue sarcomas, amputation was the standard therapeutic procedure, often resulting in significant physical and psychological morbidity to the patient. With this radical procedure, local failure is uncommon but as many as 40% of patients continued to die of metastatic disease. In the past two decades, limb-salvage approaches have drawn interest and attention, particularly with the recent advent of multimodality therapy. Treatment regimens that combine surgery, chemotherapy, and radiation have allowed treating physicians to maintain function without compromising disease control. A component of the total radiation dose can be delivered adequately as an intraoperative boost. As reported in (76), IORT is used in the multimodality treatment of sarcoma because it enables the application of high-dose radiation to the target volume using a lower EBRT dose, which results in correspondingly reduced doses to surrounding healthy tissues. Data in the literature show that IORT is able to achieve high control rates in selected cases of soft tissue sarcoma localized to the trunk or extremities.

Tran, Haas-Kogan et al. explored the efficacy of intraoperative radiation therapy (IOERT) in the treatment of soft tissue sarcomas of the extremities. Between 1995 and 2001, 17 patients received IOERT for soft tissue sarcomas of the extremities. Indications for IOERT included recurrent tumors in a previously radiated field or tumors adjacent to critical structures. IOERT used as a boost to EBRT provides excellent local control, with limited acute toxicities (51).

In the 2006 comprehensive publication of Calvo, Orecchia et al. it is reported that (6) At the University of Navarra the results obtained with an IOERT electron boost in 45 primary and recurrent sarcomas (with a mean follow-up of 93 months) showed LC rate of 80%. This data was significantly influenced by resection margin status: 88% with negative versus 57% with positive margin (p = 0.04) (52). The 7-year actuarial OS rate was 75%. The incidence of complications was acceptable (11% of peripheral neuropathy).

At the University of Munich, treatment outcome evaluation of 28 patients with high-risk soft tissue sarcoma of the extremity concluded that IOERT +/- EBRT after limb-preserving surgery achieves high LC rates, with 5-year OS and distant DFS rates of 66 and 54%, respectively. The overall actuarial recurrence rate after 5 years was 16% and the crude rate after 8 years 18%. Surgical margin status, primary versus recurrent tumor and tumor stage did not show any statistically significant influence on local recurrence rates. The risk of normal tissue toxicity was comparable to conventional limb-sparing treatment (53).
5.8. PAEDIATRIC TUMORS
As reported in (6) intraoperative radiation boost in pediatric patients may improve precision in dose deposit and protection of normal uninvolved tissues; moreover it makes feasible the design of radiation treatment programs in which the external beam component of treatment can be either omitted (in extremely radiosensitive subtypes) or decreased in total dose. A benefit in term of long-term side effects from radiotherapy might be expected.

Neuroblastoma (high-risk category) is the most common extracranial solid tumor in children and often presents as a large abdominal mass that encases major blood vessels. Treatment of neuroblastoma depends on clinical and biological risk factors. Multimodality therapy, including surgery, chemotherapy and adjuvant radiotherapy, followed by myeloablative therapy and peripheral blood stem cell transplantation appear most effective in the treatment of high-risk disease. Several studies have demonstrated the efficacy of IOERT for achieving local control in children.

It is approached with an IOERT component at UCSF (54). The more recent up-date shows 23 patients treated (18 with gross total resection) with IOERT doses in the range of 7–16 Gy and no EBRT added. Five patients developed local recurrence, all with macroscopic residual disease after resection (generally patients with upper abdominal nodal involvement). One case of narrowing of the abdominal aorta and atrophic kidney was observed.

In bone sarcomas (both Ewing and osteosarcoma) IOERT containing multimodal treatment was able to promote high LC rates (95%) together with extremity preservation surgical management (55). Three different approaches have been used: definitive IOERT without resection (56); definitive IOERT with resection (57), and intraoperative extracorporeal irradiation and reimplantation of malignant bone tumor (58). Extracorporeal IOERT is an innovative procedure in which LC seems to be higher, but some complications such as infection are still a frequent clinical event pending to be resolved (59). Moreover, combination of EBRT with IOERT is effective in incompletely resected pediatric malignancies (60).+
5.9. LUNG CANCER
As reported in (6) in addition to unresectable tumors, the intrathoracic high-risk regions for residual disease after lung cancer surgery can be treated by an IOERT electron field (61). Post-resected right and left hilair region and/or mediastinum, and posterior or apex chest wall zones are typical target areas. European investigators have used IOERT as a radiation boosting technique, complemented with EBRT alone (62) or in the context of induction systemic chemotherapy (63). Pancoast tumors seem particularly feasible for IOERT boost: long-term actuarial LC and OS rates of 91 and 56% have been reported (64). Similar results (85% of loco-regional control) have been recently observed at the Erasmus Medical Centre in Rotterdam (65). IOERT seems to be a good option for increasing LC because areas of residual microscopic disease may be irradiated without affecting critical organs to the same extent (66).

5.10. ESOPHAGEAL CANCER
Esophageal carcinoma is one of the most difficult cancerous diseases to cure, despite the common use of multimodal therapy such as surgery, radiotherapy, and chemotherapy. Tamaki, Sugimura et al. (67) started performing IOERT at Tenri Hospital in 1992 to improve the control rate in the upper abdominal lymph node area in an effort to improve overall survival rates of patients with esophageal carcinoma. Tachimori et al. focused on the anatomical lymphatic drainage system in patients with a primary lesion in the lower thoracic esophageal area and found metastasis in the perigastric lymph node area in a high proportion (65.6%) of patients with a pathological T2–4 tumor and in 39.5% of patients with a pathological T1 tumor. These findings suggest that the risk of metastasis to the perigastric lymph nodes, as well as to lower mediastinal lymph nodes, should be taken into consideration. Even after curative treatment for esophageal cancer, recurrence at the abdominal lymph node is still frequently observed and remains a critical problem. Their concern was that microscopic residual tumor in the upper abdominal area might cause abdominal recurrence, though it was performed with curative resection. Therefore, we inferred that IOERT to the upper abdominal area in combination with local curative resection would have a good effect on treatment outcome. The purpose of this study was to evaluate the effectiveness of our treatment strategy for esophageal carcinoma, especially focusing on the contribution of IOERT to overall survival and abdominal regional controllability.

A large experience in the IOERT boosting of the upper mediastinum during esophagectomy, lymphadenectomy and nerve sparing approach has been reported (68). Between 1989 and 1996, 121 patients received IOERT with doses ranging from 12 to 25 Gy followed in most cases (103) by postoperative irradiation. The number of patients by stage was: I (10), IIA (26), IIB (21), III (24) and IV (38). Four out of 18 patients (22%) treated with 25 Gy developed tracheal ulcer. No mediastinal recurrence was detected. The OS rate was 34% (cause-specific 54%).

At the University Hospital Gregorio Marañón in Madrid, an IOERT boost has been included in the context of preoperative chemo-radiation and resection. Tolerance has proven to be acceptable. IOERT was delivered to the mediastinum in all patients and to the coeliac trunk nodal regions in inferior esophageal third primary tumors. With a median follow-up of 18 months, no in-field recurrences have been observed (only marginal relapses in three cases). Actuarial 2-year OS rate was 39% (69).
5.11. PROSTATIC CANCER
In Isiort database report (76), 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 78% of cases, IORT was delivered prior to prostate removal. IORT was performed by electrons in 98% of cases, treated in five centers. In most cases, IORT was used as a boost dose prior to prostate removal. In the case of single-shot radiation, a dose of 18–21 Gy was adopted, similar to the breast cancer model. The diameter and bevel end angle of the applicators were selected on the basis of target dimensions, considering a margin of at least 5 mm around the prostate, and the energy was between 9 to 12 MeV.

In the 2006 comprehensive publication of Calvo, Orecchia et al. it is reported that (6) prostatic cancer can be approached with IOERT containing multidisciplinary treatment programs. Kato et al. have reported their experience in 54 patients (stages B2-D1) treated with fractionated EBRT (30 Gy), IOERT (25–30 Gy), pelvic lymphadenectomy and adjuvant (+/-neo) hormonal therapy (70) IOERT beam was delivered through a retropubic approach. The 5-year clinical LC and relapse-free survival rates were 83 and 74%, respectively. Rectal grade 3–4 toxicity decreased from 20 to 7% if a rectal spacer was employed. More recently, at the Regina Elena Institute in Rome, IOERT has been introduced at the time of prostatectomy over the anastomotic site in 18 patients. All received a total dose of 20–22 Gy. In vivo dosimetry estimated a dose to the rectal wall inferior to 1%. No detectable bladder, rectal or anastomotic damage has been observed. This intriguing approach should be further evaluated prospectively to define its potential in the management of localized, organ confined, prostatic cancer (71). Team in IRE and Campus Biomedical apply an α/β ratio in prostate cancer of 1.5–3 Gy, lower than that assumed for late-responsive normal tissues with the administration of a single, intraoperative dose of irradiation, that should represent a convenient irradiation modality in prostate cancer. At a median follow-up of 41 months, 24 (71%) patients were alive with an undetectable PSA value. No patients died from disease, whereas 2 patients died from other malignancies. Loco regional failures were detected in 3 (9%) patients, 2 in the prostate bed and 1 in the common iliac node chain outside the radiation field. A PSA rise without local or distant disease was observed in 7 (21%) cases. The overall 3-year biochemical progression-free survival rate was 77.3% (72).

5.12. MISCELLANEOUS INDICATIONS
Locally advanced or recurrent renal-cell cancer is considered a relatively radio-resistant histological subtype. In limited disease an IOERT boost is feasible to be integrated to the surgical management. Eble and co-workers have reported 100% LC rate in a small group (11 patients) combining resection, IOERT (15–20 Gy) and EBRT (40 Gy) (73). At a median follow-up time of 24 months, the DFS and OS rates were 34 and 47%, respectively.

Other tumors types and locations reported to be treated by IOERT have been brain tumors, head and neck cancer, metastatic spinal tumors, primary biliary tract, bladder cancer, and liver metastases (74).

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