Intraoperative Radiotherapy (IORT) is the closest interdisciplinary work between surgery and radiation oncology, aimed to increase local tumor control. The rationale is to apply a high single dose to a locally restricted volume, which could be clearly defined during surgical procedure. Dose escalation may improve tumor control, thereby sparing sensitive normal structures in close proximity by simply taking them aside.

The first attempt to bring both local modalities together is known as the “eventration therapy” and dates back to 1904-1912. The surgical procedure aimed to bring the tumor to the surface and local irradiation with orthovolt X-ray was performed on several days thereafter. In the 1960s, the real syncing combined approach, known today as the method of IORT, was introduced in Japan with a single high dose application immediately after tumor removal.

Abe et al. already started in the early 1960s with clinical trials aimed to overcome the relative dose limitation in pancreatic and gastric cancer (1-3). Initially cobalt-60 gamma rays and later electrons generated by a betatron were used. IORT doses between 25-40 Gy were given depending on the amount of residual tumor after tumor resection. The authors found that even a very high single dose of 40 Gy could not eliminate gross tumors. Subclinical tumor cells after gross tumor resection could be eliminated using a single dose of 28 Gy. Further, in the authors’ point of view, after incomplete resection a single dose of 30-35 Gy may be curative (4). On the basis of their broad experience in abdominal IORT, Abe et al. favored the combination of IORT as a boost and external beam irradiation over...
IORT alone or surgery alone in the treatment of locally advanced disease. In the authors’ opinion it is difficult to eliminate bulky tumors by single IORT doses alone and higher (cumulative) doses could be applied using external beam irradiation plus an IORT boost with a smaller risk for normal tissue damage. For the combined setting intraoperative and postoperative external doses were 10-25 and 45.8 (average) Gy by Abe et al. (4).

In the late 1970s and early 1980s several US centers included the IORT with electrons in their treatment concepts. Howard University, Washington, DC, was the first institution performing IORT in abdominal tumors with variable electron energies using a linear accelerator. In 1981 Goldson et al. reported about 19 patients with non-resectable pancreatic cancer, who were treated within a phase-I trial. As a consequence of complications such as gastrointestinal hemorrhagia or gastric ulcers the authors recommended electron IORT single doses of 20-25 Gy to the pancreas, regional nodes and duodenum as acceptable but given that the irradiated treatment volume was 100 cm³ or less (5).

Also in the 1980s, several European institutions began to gain experience with IORT using either high-energy electron beams or orthovoltage. Pioneers implementing IORT with electrons (IOERT) in Europe were mostly working groups in Pamplona (Spain), Innsbruck (Austria), Caen and Lyon (France), Groningen (Holland) and Heidelberg (Germany).

The implementation of a pooled database to record disease- and treatment-related details and outcomes of most of patients treated with IOERT (data are showed below) was an important European achievement. In 1998 the International Society of IORT (ISIORT) was founded and the first ISIORT-meeting took place in Pamplona (Spain). Calvo et al. preferred IOERT doses of 10-20 Gy and external beam doses 45-54 Gy (6). The IORT dose depends on the volume of residual tumor cells and varies from 10-12.5 Gy for microscopic disease or less and 15-20 Gy for gross residual disease (6).

Currently, many entities, such as abdominal or pelvic cancers (i.e., pancreatic, gynecological or rectal), sarcomas (limb or retroperitoneal) or breast cancers, are treated with IOERT, mostly in combination with external beam radiotherapy (EBRT). The most frequently treated entities are rectal cancers, sarcomas and breast cancers.

**Technical principals and developments**

All IORT techniques using either electrons (IOERT), low-energy X-rays or HDR-brachytherapy with Iridium 192 have specific advantages and disadvantages. One relevant physical advantage using electrons is the depth-dose distribution with high dose homogeneity within the target volume and a sharp dose fall-off (7). The depth-dose is accurately assessable by adjusting the electron energy. Using between 4 and 12 MeV the depth of the 90%-isodose ranges approximately from 15 to 40 mm, depending on field size and beam angle.

Several technical options are available performing an IORT with electrons. In principle, IOERT could be performed with a conventional, non-dedicated Linear accelerator (Linac). In such situation narcotized patients must be transported from the operating theater to the radiation oncology room. This approach is very elaborate and seems to be a disincentive in regard to a further propagation of this technique. These limitations had been overcome in several hospitals using dedicated IOERT facilities. In such units, the Linac is firmly installed into the operating room.

In the past, a more attractive approach became available, the mobile Linac. Mobile Linacs, such as Mobetron® (Intra Medical Corp., Sunnyvale, California, USA) or Novac® (Sordina IORT Technologies S.p.A, Vicenza, Italy) are cost-efficient compact machines movable within the operating room by a built-in electric-drive. The machines are very flexible and are able to apply the electron beam to nearly all requested anatomical regions. The Linacs generate only electron energies in a range of 6-12 MeV (Mobetron®) and 4-10 MeV (Novac®). The effort of a specific shielding is fairly smaller as using Linacs generating MeV photons.

**Rectal cancer**

The treatment of choice for locally advanced rectal cancer is neoadjuvant EBRT of the pelvis with a dose of about 50 Gy with concurrent fluoropyrimidine-based chemotherapy and followed by surgical removal and further adjuvant fluoropyrimidine-chemotherapy. This approach leads to very low 10-year local recurrence rates (8). An important milestone in decreasing the relapse rate was the implementation of a total mesorectal excision (TME) (9,10). It is easy to comprehend that dose escalation may have a low relative influence even on low recurrence rates, as was confirmed by a French randomized trial comparing surgery with and without IOERT with 18 Gy (11). All patients had a T3/T4 or N+ rectal cancer and were treated with a preoperative irradiation of 40 Gy. The 5-year local relapse...
rate was 7.2% without and 8.2% after additional IOERT. Bearing a higher local recurrence rate, IOERT seems to be an option for patients with locally very advanced rectal cancer. In 2010 Kusters et al. reported the results of a European pooled data analysis from an IOERT-containing multimodal approach for locally advanced rectal cancer (12). The patients included in this analysis had a nearly or involved mesorectal fascia or T4-tumors. The IOERT- and EBRT-doses were 10–12.5 and 45–50.4 Gy, respectively. Despite the very high-risk situation, a promising low 5-year recurrence rate of 5.5% could be achieved (12).

For patients suffering from a localized recurrent rectal cancer, IOERT provides an additional option, even after prior pelvic irradiation. Due to the widespread use of a multimodal primary treatment, the occurrence of an isolated recurrence confined to the pelvis is seen fortunately seldom today. But in the event of tumor regrowth, debilitating symptoms arise from infiltration of bony structures or intrapelvic structures. In patients without prior radiotherapy, 3-4-year relapse-free survival rates of 48-49% are achievable using a multimodal approach including preoperative external radiotherapy and IOERT (13,14). Patients with rectal cancer recurrence who had prior radiotherapy and could be treated with surgery and sole IOERT revealed a marked decrease in prognosis. Pezner et al. reported a 3-year local control rate of 55% in a small patient cohort (15). In patients with fixed and/or bulky pelvic tumors the local control rate decreased to 19% at 12 months.

**Retroperitoneal and limb soft tissue sarcomas**

Soft tissue sarcomas are a heterogeneous group of malignant tumors, which can be present on nearly all body areas. About 60% of all soft tissue sarcomas arise at the extremities and 14% are diagnosed within the abdominal cave (16,17).

In the 1980s radical strategies with limb-amputation were replaced by limb-conserving approaches, resulting in a multimodal treatment approach including limb-conserving surgery, irradiation and for some entities additional chemotherapy. With modern limb-conserving strategies local control rates of more than 75% are achievable (18,19). The role of irradiation in limb-conserving treatment could be demonstrated by a randomized trial. Local control was significantly improved by adding adjuvant radiotherapy to limb-sparing surgery (19). A SEER-analysis yielded in addition a survival benefit in high-grade sarcomas after additional radiotherapy (3-year overall survival 73% vs. 63%) (20).

Regarding late adverse effects, percutaneous fractionated radiotherapy in a preoperative setting may be more favorable. In a study by O’Sullivan et al., which addressed the influence of preoperative (50 Gy) versus postoperative (66 Gy) radiotherapy on the occurrence of edema (23.2% vs. 15.5%) and joint stiffness (23.2% vs. 17.8%) (21), preoperative irradiation yielded less late adverse effects. Nevertheless wound complications were more common in the preoperative radiotherapy group. Overall, local relapse and disease free survival rates did not differ between both cohorts. A reduction in radiotherapy dose (50 Gy) reduced late toxicity (21). In the same way, the potential risk of bone fracture will be reduced using moderate external beam doses. Dickie et al. reported a lower risk of bone fractures if the bone volume receiving ≥40 Gy was <64% (22).

The well-balanced combination of a locally restricted boost dose with a moderate percutaneous fractionated dose may reduce long-term adverse effects by less dose volume load without compromising the patient’s prognosis. In a study by van Kampen et al. 53 patients with extremity sarcomas were treated with a moderate IOERT dose (median 15 Gy) followed by an equally moderate EBRT dose of 46 Gy (23). The overall survival and actuarial tumor control rates were 84% and 90% after five years. Five patients developed Grade 3 fibrosis and one patient developed Grade 4 fibrosis. The authors concluded that a well-balanced dose-volume load provides excellent local control and decreases long-term adverse effects (23). As expected, the high dose volume was correlated with late severe adverse effects. An IOERT volume of 210 cm³ conveyed a 5% risk of severe fibrosis. The risk of grade 3 or 4 fibrosis increased to 50% if a volume of 420 cm³ was irradiated. Comparable results were published by Azinovic et al. (24) or Tran et al. (17).

Retroperitoneal sarcomas are a big challenge. Most of them are huge and adjacent to vital radiosensitive normal structures at the time of diagnosis. Surgical removal is the cornerstone, but microscopically complete resections are often not achievable. Stojadinovic et al. from the Memorial Sloan-Kettering Cancer Center analyzed 2,084 primary soft tissue sarcomas regarding the prognostic influence of the resection margins (25). In only 55% of 229 retroperitoneal sarcomas microscopically clear margins were seen. The retroperitoneal site was an independent factor for positive margins in this analysis.

Valid data to analyze the role of preoperative versus postoperative radiotherapy are not available and must be gathered (26,27). An EORTC study (EORTC 62092-
randomized trials could demonstrate that a dose increase of 10-16 Gy in 2 Gy daily fractions within the tumor bed significantly increase local tumor control (36-38). However, the percutaneous boost dose application could impair the cosmetic result. The rate of grade 3 and 4 fibrosis increased from 1.6% to 4.4% (37), the rate of all grades of telangiectasia from 5.9% to 12.4% (38). In addition, the treatment efficacy may be impaired due to a geographical miss of the real tumor bed. During the healing process a relevant change of the tumor bed position and volume was observed (39,40). A boost dose volume definition based on clinical parameters was associated with a geographical miss of 37.5-56% compared to a surgical clip oriented approach (41-43). But even a surgical clip oriented approach is critical because of the potential risk of clip migration (44-46).

IORT within the concept of BCT in breast cancer patients is an innovative treatment option, which influenced clinical practice in the last years. Two distinctive indications could be established. Locally restricted dose escalation combined with WBI or a partial breast irradiation (PBI). Considering the previously mentioned limitations of percutaneous boost dose application, the advantages of IORT are obvious. Immediately after tumor removal, the tumor bed could be clearly defined by the surgeon and radiation oncologist. Consequently, the radiation tube is placed “online” without geographic miss. The skin and subcutaneous tissue could be placed outside the irradiation field, resulting in a marked decrease in the rates of telangiectasia, hyperpigmentation and subcutaneous fibrosis (47-49).

A locally restricted intraoperative dose escalation combined with WBI is generally accepted by analogy with the percutaneous fractionated boost dose application with electrons (34,35). A European pooled data analysis of 1,031 patients yields highly encouraging results after IOERT (50). Patients had a single shot boost with a median dose of 9.7 Gy, added to a fractionated WBI with 50-54 Gy. After a median follow-up of 52 months a very high local control rate of 99.4% was observed. The 7-year DFS and OS were 95.2% and 90.9%. The favorable efficacy of an IOERT-boost compared to an EBRT-boost was shown by Reitsamer et al. They performed a sequential intervention study including 378 patients (51). A 4-year local relapse and distant relapse rate of 4.3% vs. 0% and 7.9% vs. 1.1% was reported in favor of an IOERT-compared to an EBRT-boost. Besides efficacy, a single shot intraoperative electron boost has advantages in patient comfort and cosmesis. The radiotherapy course is shortened by 5–8 days. In the EORTC “boost vs. no boost” trial an EBRT-boost led to a
good or very good cosmesis in 71% of boost-patients and in 86% of patients without a boost (52). In an IOERT-boost study by Lemanski et al. all patients assessed their own cosmetic results as good or very good after a median follow-up of 9.1 years (53).

What could be a disadvantage? It must be considered that the definite pathological statement on clear specimen margins will not be available at the time of IORT. An additional excision will remove irradiated tumor bed tissue, intended to treat as an additional safety margin after microscopically clear margins. One major factor is the presence of an extensive intraductal component (EIC), which is associated with a ductal carcinoma in situ (DCIS), seen in a distant position from the primary tumor in 44% of cases (54). EIC with additional resections and therefore removal of irradiated tumor bed tissue is not uncommon (55). In our patient cohort an additional resection because of positive resection margins associated with DCIS was necessary in 13% of cases (56). In our opinion in patients with a preoperatively detected EIC IORT should be avoided. Also, an invasion of the skin or directly subcutaneous tissue is an exclusion criterion (57). In such patients, we should perform an external beam boost including the skin.

Considering that most of the in-breast tumor recurrences are located in or near to the initial tumor site (36,58-61) PBI as the sole radiotherapy treatment modality is of large interest. Different PBI techniques, such as an IORT with electrons or 50 kV X-rays (Intrabeam®), the interstitial multicatheter or balloon catheter (Mammosite®) brachytherapy or the 3D conformal EBRT are in clinical use [overview in (62,63)]. No superiority could be shown for any of the above-mentioned techniques to date.

Only one randomized trial compared an intraoperative electron PBI with a standard fractionated WBI, published recently by Umberto Veronesi et al. (64). Overall 1,305 patients were included. Patients randomized to the IOERT-group received a single dose of 21 Gy to the tumor bed. After a median follow-up of 5.8 years, 35 patients in the IOERT- and 4 patients in the EBRT-group suffered an in-breast tumor recurrence. The 5-year local relapse rate was 4.4% and 0.4% in favor for the group, which was treated by WBI and percutaneous fractionated boost dose. No significant differences were seen according to overall or distant metastases free survival.

Comprehensively the authors conclude that IOERT as PBI should be restricted to suitable patients, once characteristics defining suitability have been defined. Further, the authors highlight a main problem caused by the absence of the final pathological examination complicating the exact patient selection. Defining valid selection criteria for those patients having a maximum benefit is nevertheless the main goal to implement the PBI in the concept of BCT of breast cancer.

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