Intraoperative Radiotherapy with electrons

Marc D. Piroth[1], Michael J. Eble[2]

[1]Department of Radiation Oncology, HELIOS Hospital Wuppertal, Wuppertal, Germany; [2]Department of Radiation Oncology, University Hospital RWTH Aachen, Aachen, Germany

Correspondence to: Marc D. Piroth has made substantial contributions to the conception, analysis and interpretation of data and drafted the manuscript. Michael J. Eble has also made substantial contributions to the conception, analysis and interpretation of data. Marc D. Piroth, M.D. Department of Radiation Oncology, HELIOS Hospital Wuppertal, Heussnerstrasse 40, 42283 Wuppertal, Germany. Email: marc.piroth@helios-kliniken.de.

Abstract: Intraoperative Radiotherapy (IORT) with electrons allow to apply a high single dose to a locally restricted volume, which could be clearly defined during surgical procedure. Especially in cases with relative dose limitation using external beam radiotherapy (EBRT) only due to normal structures the IORT technique is meaningful. Many retrospective or non-randomized data support the use of IORT but prospective randomized data are mostly not available. Intraoperative electron radiotherapy (IOERT) seems to be a valide option for patients with locally very advanced or recurrent rectal cancer. In retroperitoneal sarcomas the advantages of IORT are clearly recognizable shown in a randomized-trial. The IOERT patients had a significantly lower local-regional relapse rate. Concerning breast cancer treatment the favorable efficacy of an IOERT-boost compared to an EBRT-boost could be shown in a sequential intervention study. Also, in a European pooled data analysis including 1,031 patients highly encouraging results after IOERT were published. An open question is the value of the sole PBI in breast cancer patients in the context of breast conservation. The prospective and randomized ELIOT-trial addressing this question show higher local recurrences in the IORT only group and led to the study group's statement that IOERT as partial breast irradiation (PBI) should be restricted to suitable patients, once characteristics defining suitability have been defined.

Keywords: Intraoperative radiotherapy (IORT); electron intraoperative radiotherapy (electron IORT); IOERT

Submitted Feb 17, 2014. Accepted for publication Mar 11, 2014.
doi: 10.3978/j.issn.2218-676X.2014.03.02
View this article at: http://www.thetcr.org/article/view/2367/2962

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.

History of electron IORT and dose findings

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 cm^3 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 cm^3 conveyed a 5% risk of severe fibrosis. The risk of grade 3 or 4 fibrosis increased to 50% if a volume of 420 cm^3 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-

22092; "STRASS-study") comparing a preoperative EBRT followed by surgery with surgery alone is ongoing. One of the most relevant problems for performing safe irradiation is the close contact to more radiosensitive structures like small bowel, kidney or liver. Despite modern techniques such as intensity-modulated radiotherapy, an effective radiation dose of up to 60 Gy is not achievable in most patients. Because of this dilemma, many centers omit radiotherapy in retroperitoneal sarcomas (28). Recently, a SEER analysis from 762 patients was published by Choi *et al.* (29). Overall, 558 patients had surgery only and 204 had surgery with radiation. No survival difference between propensity score-matched patients receiving radiotherapy versus no radiotherapy was seen.

In retroperitoneal sarcomas the advantages of IORT are clearly recognizable. The positive prognostic impact of IORT with electrons in primary retroperitoneal sarcomas could be demonstrated by the National Cancer Institute, which conducted the only randomized trial (30) so far. In this trial all patients had gross total resection, mostly with microscopically residual tumor. Patients had either a postoperative EBRT with 50-55 Gy or an IOERT with 20 Gy followed by an EBRT of 35-40 Gy. The IOERT group had a significantly lower local-regional relapse rate (20% *vs.* 80%) after a median follow-up of five years. The median survival was not significantly different (45 *vs.* 52 months). The improvement in local control was supported in a retrospective analysis from patients treated at the Mayo Clinic. The analysis comprises data from 87 patients with primary (43 pts.) or locally recurrent (44 pts.) retroperitoneal or pelvic sarcoma (31). An EBRT dose of 48.6 and 45 Gy was given for patients with primary and locally recurrent tumors, respectively and combined with a median IOERT dose of 15 Gy. After a minimum follow-up of one year 7% of primary and 39% of recurrent tumors relapsed. The 5-year overall survival rate was 52% and 42%.

Calvo *et al.* stated, that based on the NCI trial the use of adjuvant EBRT without IOERT after marginal resection could be questioned because of the high rate of tumor bed relapse in the EBRT only group (32).

Breast cancer

Adjuvant external beam irradiation of the whole breast irradiation (WBI) is an obligatory part of breast conserving treatment (BCT). A radiation dose of 50-50.4 Gy in daily fractions of 1.8-2 Gy is recommended (33-35). Two 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 balloncatheter (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.

Comprehensibly 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.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Frederik Wenz and Elena Sperk) for the series "Intraoperative Radiotherapy" published in *Translational Cancer Research*. The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.3978/j.issn.2218-676X.2014.03.02). The series "Intraoperative Radiotherapy" was commissioned by the editorial office without any funding or sponsorship. Marc D. Piroth and Michael J. Eble state explicitely, that there are no actual or potential conflicts of interest in relation to this article.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Abe M, Nishimura Y, Shibamoto Y. Intraoperative radiation therapy for gastric cancer. World J Surg 1995;19:544-7.

2. Abe M, Fukuda M, Yamano K, et al. Intra-operative irradiation in abdominal and cerebral tumours. Acta Radiol Ther Phys Biol 1971;10:408-16.
3. Abe M, Takahashi M, Yabumoto E, et al. Clinical experiences with intraoperative radiotherapy of locally advanced cancers. Cancer 1980;45:40-8.
4. Abe M, Shibamoto Y, Takahashi M, et al. Intraoperative radiotherapy in carcinoma of the stomach and pancreas. World J Surg 1987;11:459-64.
5. Goldson AL, Ashaveri E, Espinoza MC, et al. Single high dose intraoperative electrons for advanced stage pancreatic cancer: phase I pilot study. Int J Radiat Oncol Biol Phys 1981;7:869-74.
6. Calvo FA, Meirino RM, Orecchia R. Intraoperative radiation therapy first part: rationale and techniques. Crit Rev Oncol Hematol 2006;59:106-15.
7. Nairz O, Deutschmann H, Kopp M, et al. A dosimetric comparison of IORT techniques in limited-stage breast cancer. Strahlentherapie und Onkologie : Strahlenther Onkol 2006;182:342-8.
8. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 2012;30:1926-33.
9. Porter GA, Soskolne CL, Yakimets WW, et al. Surgeon-related factors and outcome in rectal cancer. Ann Surg 1998;227:157-67.
10. Hermanek P, Hermanek P, Hohenberger W, et al. The pathological assessment of mesorectal excision: implications for further treatment and quality management. Int J Colorectal Dis 2003;18:335-41.
11. Dubois JB, Bussieres E, Richaud P, et al. Intra-operative radiotherapy of rectal cancer: results of the French multi-institutional randomized study. Radiother Oncol 2011;98:298-303.
12. Kusters M, Valentini V, Calvo FA, et al. Results of European pooled analysis of IORT-containing multimodality treatment for locally advanced rectal cancer: adjuvant chemotherapy prevents local recurrence rather than distant metastases. Ann Oncol 2010;21:1279-84.
13. Eble MJ, Lehnert T, Treiber M, et al. Moderate dose intraoperative and external beam radiotherapy for locally recurrent rectal carcinoma. Radiother Oncol 1998;49:169-74.
14. Ferenschild FT, Vermaas M, Verhoef C, et al. Abdominosacral resection for locally advanced and recurrent rectal cancer. Br J Surg 2009;96:1341-7.
15. Pezner RD, Chu DZ, Ellenhorn JD. Intraoperative radiation therapy for patients with recurrent rectal and sigmoid colon cancer in previously irradiated fields. Radiother Oncol 2002;64:47-52.
16. Brennan MF, Casper ES, Harrison LB, et al. The role of multimodality therapy in soft-tissue sarcoma. Ann Surg 1991;214:328-36; discussion 36-8.
17. Tran QN, Kim AC, Gottschalk AR, et al. Clinical outcomes of intraoperative radiation therapy for extremity sarcomas. Sarcoma 2006;2006:91671.
18. O'Sullivan B, Wylie J, Catton C, et al. The local management of soft tissue sarcoma. Semin Radiat Oncol 1999;9:328-48.
19. Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 1998;16:197-203.
20. Koshy M, Rich SE, Mohiuddin MM. Improved survival with radiation therapy in high-grade soft tissue sarcomas of the extremities: a SEER analysis. Int J Radiat Oncol Biol Phys 2010;77:203-9.
21. O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet 2002;359:2235-41.
22. Dickie CI, Parent AL, Griffin AM, et al. Bone fractures following external beam radiotherapy and limb-preservation surgery for lower extremity soft tissue sarcoma: relationship to irradiated bone length, volume, tumor location and dose. Int J Radiat Oncol Biol Phys 2009;75:1119-24.
23. van Kampen M, Eble MJ, Lehnert T, et al. Correlation of intraoperatively irradiated volume and fibrosis in patients with soft-tissue sarcoma of the extremities. Int J Radiat Oncol Biol Phys 2001;51:94-9.
24. Azinovic I, Martinez Monge R, Javier Aristu J, et al. Intraoperative radiotherapy electron boost followed by moderate doses of external beam radiotherapy in resected soft-tissue sarcoma of the extremities. Radiother Oncol 2003;67:331-7.
25. Stojadinovic A, Leung DH, Hoos A, et al. Analysis of the prognostic significance of microscopic margins in 2,084 localized primary adult soft tissue sarcomas. Ann Surg 2002;235:424-34.
26. Mullinax JE, Zager JS, Gonzalez RJ. Current diagnosis and management of retroperitoneal sarcoma. Cancer Control 2011;18:177-87.
27. Schwarzbach MH, Hohenberger P. Current concepts in the management of retroperitoneal soft tissue sarcoma.

Recent Results Cancer Res 2009;179:301-19.
28. Lewis JJ, Leung D, Woodruff JM, et al. Retroperitoneal soft-tissue sarcoma: analysis of 500 patients treated and followed at a single institution. Ann Surg 1998;228:355-65.
29. Choi AH, Barnholtz-Sloan JS, Kim JA. Effect of radiation therapy on survival in surgically resected retroperitoneal sarcoma: a propensity score-adjusted SEER analysis. Ann Oncol 2012;23:2449-57.
30. Sindelar WF, Kinsella TJ, Tepper JE, et al. Randomized trial of intraoperative radiotherapy in carcinoma of the stomach. Am J Surg 1993;165:178-86; discussion 86-7.
31. Petersen IA, Haddock MG, Donohue JH, et al. Use of intraoperative electron beam radiotherapy in the management of retroperitoneal soft tissue sarcomas. Int J Radiat Oncol Biol Phys 2002;52:469-75.
32. Calvo FA, Meirino RM, Orecchia R. Intraoperative radiation therapy part 2. Clinical results. Crit Rev Oncol Hematol 2006;59:116-27.
33. Goldhirsch A, Wood WC, Gelber RD, et al. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol 2007;18:1133-44.
34. Kurtz J, Party EW. The curative role of radiotherapy in the treatment of operable breast cancer. Eur J Cancer 2002;38:1961-74.
35. Sedlmayer F, Sautter-Bihl ML, Budach W, et al. DEGRO practical guidelines: radiotherapy of breast cancer I: radiotherapy following breast conserving therapy for invasive breast cancer. Strahlenther Onkol 2013;189:825-33.
36. Bartelink H, Horiot JC, Poortmans P, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. N Engl J Med 2001;345:1378-87.
37. Bartelink H, Horiot JC, Poortmans PM, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. J Clin Oncol 2007;25:3259-65.
38. Romestaing P, Lehingue Y, Carrie C, et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. J Clin Oncol 1997;15:963-8.
39. Hurkmans C, Admiraal M, van der Sangen M, et al. Significance of breast boost volume changes during radiotherapy in relation to current clinical interobserver variations. Radiother Oncol 2009;90:60-5.
40. Jacobson G, Betts V, Smith B. Change in volume of lumpectomy cavity during external-beam irradiation of the intact breast. Int J Radiat Oncol Biol Phys 2006;65:1161-4.
41. Denham JW, Carter ML, Gill PG. Conservative treatment of breast cancer--where should the booster dose go? Int J Radiat Oncol Biol Phys 1988;14:399-400.
42. Bedwinek J. Breast conserving surgery and irradiation: the importance of demarcating the excision cavity with surgical clips. Int J Radiat Oncol Biol Phys 1993;26:675-9.
43. Harrington KJ, Harrison M, Bayle P, et al. Surgical clips in planning the electron boost in breast cancer: a qualitative and quantitative evaluation. Int J Radiat Oncol Biol Phys 1996;34:579-84.
44. Bernaerts A, De Schepper A Jr, Van Dam P, et al. Clip migration after vacuum-assisted stereotactic breast biopsy: a pitfall in preoperative wire localization. JBR-BTR 2007;90:172-5.
45. Parikh J. Clip migration within 15 days of 11-gauge vacuum-assisted stereotactic breast biopsy. AJR Am J Roentgenol 2005;184:S43-6.
46. Kass R, Kumar G, Klimberg VS, et al. Clip migration in stereotactic biopsy. Am J Surg 2002;184:325-31.
47. Intra M, Gatti G, Luini A, et al. Surgical technique of intraoperative radiotherapy in conservative treatment of limited-stage breast cancer. Arch Surg 2002;137:737-40.
48. Orecchia R, Ciocca M, Tosi G, et al. Intraoperative electron beam radiotherapy (ELIOT) to the breast: a need for a quality assurance programme. Breast 2005;14:541-6.
49. Reitsamer R, Peintinger F, Sedlmayer F, et al. Intraoperative radiotherapy given as a boost after breast-conserving surgery in breast cancer patients. Eur J Cancer 2002;38:1607-10.
50. Sedlmayer F, Fastner G, Merz F, et al. IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: results of an ISIORT pooled analysis. Strahlenther Onkol 2007;183 Spec No 2:32-4.
51. Reitsamer R, Peintinger F, Kopp M, et al. Local recurrence rates in breast cancer patients treated with intraoperative electron-boost radiotherapy versus postoperative external-beam electron-boost irradiation. A sequential intervention study. Strahlenther Onkol 2004;180:38-44.
52. Vrieling C, Collette L, Fourquet A, et al. The influence of patient, tumor and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC 'boost vs. no boost' trial. EORTC Radiotherapy and Breast Cancer Cooperative Groups. Radiother Oncol 2000;55:219-32.
53. Lemanski C, Azria D, Thezenas S, et al. Intraoperative radiotherapy given as a boost for early breast cancer: long-

term clinical and cosmetic results. Int J Radiat Oncol Biol Phys 2006;64:1410-5.
54. Holland R, Connolly JL, Gelman R, et al. The presence of an extensive intraductal component following a limited excision correlates with prominent residual disease in the remainder of the breast. J Clin Oncol 1990;8:113-8.
55. Dzierzanowski M, Melville KA, Barnes PJ, et al. Ductal carcinoma in situ in core biopsies containing invasive breast cancer: correlation with extensive intraductal component and lumpectomy margins. J Surg Oncol 2005;90:71-6.
56. Piroth MD, Heindrichs U, Pinkawa M, et al. Intraoperative Radiotherapy (IORT) with Electrons for Breast Cancer - Our Experience, Current Considerations and Review of the Literature. Geburtshilfe und Frauenheilkunde 2010;70:219.
57. Gatzemeier W, Orecchia R, Gatti G, et al. Intraoperative radiotherapy (IORT) in treatment of breast carcinoma--a new therapeutic alternative within the scope of breast-saving therapy? Current status and future prospects. Report of experiences from the European Institute of Oncology (EIO), Mailand. Strahlenther Onkol 2001;177:330-7.
58. Clarke DH, Le MG, Sarrazin D, et al. Analysis of local-regional relapses in patients with early breast cancers treated by excision and radiotherapy: experience of the Institut Gustave-Roussy. Int J Radiat Oncol Biol Phys 1985;11:137-45.
59. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233-41.
60. Morrow M. Rational local therapy for breast cancer. N Engl J Med 2002;347:1270-1.
61. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227-32.
62. Njeh CF, Saunders MW, Langton CM. Accelerated Partial Breast Irradiation (APBI): A review of available techniques. Radiat Oncol 2010;5:90.
63. Sauer G, Strnad V, Kurzeder C, et al. Partial breast irradiation after breast-conserving surgery. Strahlenther Onkol 2005;181:1-8.
64. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol 2013;14:1269-77.

Cite this article as: Piroth MD, Eble MJ. Intraoperative radiotherapy with electrons. Transl Cancer Res 2014;3(2):167-174. doi: 10.3978/j.issn.2218-676X.2014.03.02