INTRAOPERATIVE RADIOTHERAPY (IORT)

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Intraoperative radiotherapy (IORT) remains a fascinating and sophisticated method of dose delivery with utmost precision, even in times of a growing number of competing techniques for dose escalation. For a long time, its use was restricted to just a few institutions due to high logistical requirements. The development of mobile linacs, as well as alternative technical approaches, has opened the way for its rapid broad application and integration into routine treatment. Founded in 2006, ISIORT Europe alternates its meetings with the biennial ISIORT International congresses. Originally organised jointly with the GEC-ESTRO-Group, these conferences are now hosted under the auspices of the ESTRO Forum, and after London 2011 and Geneva 2013, the 2015 meeting took place in Barcelona for the third time as a track within the main programme.

During the meeting, the board of ISIORT Europe was re-elected and is now represented by Robert Krempien (Berlin, Germany) as chair for the next two years and Alfredo Polo (Madrid, Spain) as chair-elect.

Over 140 participants followed a broad spectrum of reports on IORT in breast cancer, sarcoma, pelvic tumours, and palliative indications. A separate part covered physics and dosimetry, introduced by Catherine Philippson (Brussels, Belgium).

Since 2007, ISIORT Europe has collected data on patients treated with various IORT concepts in a special web-based data platform. Marco Krengli (Novara, Italy) presented an update of a big joint analysis on technical and epidemiologic details. Between 1992 and 2014, 80% of all documented cases, corresponding to almost 8,500 IORT procedures, were performed in breast cancer patients, highlighting its growing clinical relevance.

IORT IN BREAST CANCER

Frederik Wenz (Mannheim, Germany) gave an excellent opening lecture about the biology of high single doses in the light of new molecular pathologic research, with breast cancer serving as model tumour.

New or updated data were available for both IORT as a boost or as a single treatment. The latter was presented by Jay Vaidya (London, UK) with new aspects from the TARGIT-A trial (50) KV-Orthovolt x-ray single treatment to the tumour bed only, compared to standard ▼

whole breast irradiation (WBI) following breast conserving surgery, investigating the frequency of out-quadrant recurrences after IORT compared to WBI.

This analysis was prompted by the observation that pathological work-up of breast tissues after radical mastectomies revealed tumour foci in 63% of all cases outside the primary tumour site and, out of these, 80% in other quadrants, thus awaiting more out-quadrant relapses without the cell sterilising effect of WBI. This interim analysis included 793 IORT and 935 WBI patients.
In the IORT-only group, recurrences in the former index quadrant, out-quadrants and new primaries in the contralateral breast occurred in seven, two and six patients, respectively. In comparison, in the WBI-group, two out-quadrant relapses and five new contralateral cancers were observed. Whether this reflects that out-quadrant foci are unaffected by WBI, sufficiently treated by systemic treatment, or occurring later over time, has to be clarified in longer follow up.

Long-term results of 64 patients treated with IORT as a sole treatment either with electrons (IOERT) or 200 kv Orthovolt x-rays up to dosages of 15-21 Gy were presented by Kathleen Horst for the Stanford group (USA). Eighty-one percent of these patients received adjuvant systemic medication (endocrine/chemotherapy). After a median follow-up of 88 months (range 1-144) two ipsilateral breast tumour recurrences (IBTR) occurred, accounting for an IBTR-rate of 1.6% after six years. Age <50 years, nodal involvement and lack of any adjuvant systemic therapy were ruled out as negative predictors for IBTR.

For testing the combination of boost IOERT (10 Gy) with hypofractionated WBI (15 x 2.7 Gy), a prospective ISIORT multicentre trial (HIOB) was initiated in 2011 for stage I/II breast cancer. The trial design follows a sequential probability ratio test (SPRT), defining annual in-breast recurrence rates as benchmarks for successful treatment. Beside tumour-related endpoints, major emphasis is put on treatment tolerance and cosmetic outcome. As of August 2014, within ten active institutions 645 patients have been recruited so far. Gerd Fastner (Salzburg, Austria) presented an interim analysis up to March 2015. At a median follow up of 13.5 months (range 1-48) CTC 0/I acute reactions were observed in 92% and 94% of the population evaluated directly after the end of WBI and four weeks later, respectively. G0-I late reactions (LENT-SOMA) were observed in 97%. Cosmesis was repeatedly assessed, beginning in the fourth or fifth months and annually thereafter. Three-year data showed satisfactory (excellent or good), acceptable (excellent, good or moderate) and unacceptable results (bad or complications) by subjective evaluations in 85%, 98% and 2%, respectively, and by objective ratings in 78%, 95%, and 5%. No complications have been observed, and in-breast recurrences have not been noted so far.

The IOERT-Boost concept was investigated in terms of local control (LCR) and survival rates in triple negative breast cancer (TNBC) patients, who show a higher probability of local relapse and worse survival compared to other breast cancer subtypes. Gerd Fastner (Salzburg, Austria) presented results of a retrospective analysis of 71 TNBC patients treated between 1998 and 2005. All patients were treated after breast conserving surgery (BCS) and boost IOERT (med. Dmax 9.6 Gy) with WBI in conventional fractionation up to median total doses of 54 Gy. Patients were classified into TNBC-sub-groups defined as five-marker negative phenotype (5-NP) and core basal (CB) and grouped along tumour grading G1/2 and G3, resulting in four sub-groups. After a median follow up of 97 months, an actuarial LCR of 89% at eight years was reported. Five in-breast recurrences occurred (7%), all in the former index quadrant. Sub-group analysis revealed G1/2 as associated by trend with higher LCR than ▼

G3, irrespective of further TNBC sub-classification (5-NP or CB). Disease specific survival (DSS), overall survival (OS) and metastases free survival (MFS) showed a trend for superior outcome in 5-NP in comparison to CB, independently of the respective tumour grading. Interestingly, only by comparing DSS of the subgroup 5-NP/G3 to CB/G1/2, significance was reached (90 vs. 54%, p=0.03). Possible predictors for local failure were Ki 67 ≥ 20%, G3 and IOERT with electron tube diameters < 6 cm.

In summary, IORT in breast cancer seems to be more and more established as alternative treatment option either as boost technique for all risk constellations (also for high risk sub-groups as shown for TNBC) or as sole treatment in very selected low risk cases. Treatment tolerance is confirmed as high, also in combination with new hypofractionated WBI regimens after a short follow-up.

Opening ceremony at the 3rd ESTRO Forum, Philip Poortmans introducing ISIORT

IORT IN OTHER REGIONS

Sarcomas, rectal cancer and genitourinary tumours

Robert Krempien (Berlin, Germany) gave an overview lecture about IORT for extremity soft tissue sarcomas. Based on the results of a previous pooled analysis of 2009, Falk Roeder (Heidelberg, Germany), reported on a recent follow-up analysis on a sub-group of this cohort, restricted to those patients who received also external beam radiation (EBRT) either preceding or following boost IORT after gross total tumour-resection, leaving 250 patients. Kaplan Meier calculation was performed for local control, distant control and overall survival and univariate/multivariate subgroup analyses to reveal possible negative prognostic factors, again revealing close margin status as most predictive for subsequent local relapse. ▼

Claudio Sole (Chile) reported on the experience of the Gregorio Maranon Clinics (Madrid, Spain). Seventy-one patients with primary or recurrent paediatric Ewing Sarcoma (EWS, n=37) or rhabdomyosarcoma (RMS, n=34), who received IOERT (median dose 10 Gy) with or without EBRT (median dose 40 Gy) after conservative tumour resection, achieved 10-year rates for local control, disease-free survival, and overall survival of 74%, 57%, and 68%, respectively. Median follow up was 72 months (range 4-310), severe chronic toxicity (grade ≥ 3) was observed in nine patients (13%).

From the same institute, recent data for oligo-recurrent sarcoma (ORS, n=103), gynaecological (ORGC, n=61) or rectal cancer (ORRC, n=60) were presented, which were treated with IOERT (median 12.5 Gy, range 10-15 Gy) during surgical resection, with or without EBRT (range 30.6 – 50.4 Gy). After median follow-up periods of 55 months (range 2-189 months) five-year rates for locoregional control (LRC) and overall survival (OS) amounted to 60% and 65%, 52% and 43%, 43% and 42% for ORS, ORRC and ORGC respectively. R1 resection, additional EBRT at time of recurrence and no tumour fragmentation turned out to be significant for LRC in multivariate analyses.

Harm Rutten (Eindhoven, The Netherlands) gave a comprehensive overview lecture on the potential of IORT in locally advanced and/or recurrent rectal cancer. A series of 77 Spanish patients was presented by Claudio Sole, all of them with advanced T4 rectal cancer, treated with neoadjuvant chemoradiotherapy, surgery and IOERT. Five-year locoregional-control, disease-free survival and overall survival rates were reported to be encouragingly high, with 84%, 68% and 65%, respectively, after a median follow-up of 62.8 months (range 4-198 months).

The spectrum on IORT for pelvic tumours was completed by Marco Krengli (Novara, Italy), elucidating its possible role in prostate cancer.

In summary, IORT in primary or recurrent sarcomas was confirmed to be an effective and safe treatment option, and also for paediatric malignancies. Margin status turned out to be of highest relevance for local control. Further intensified research is needed to evaluate the appropriate sequences of local treatment (IOERT, EBRT, surgery) and chemotherapy. Results of such a multimodality treatment for T4 rectal cancer seemed to be promising.

Palliation

Reports of IORT for palliative indications, such as for bone or soft tissue metastases, are quite new. Experiences of treating bone metastases of the vertebral body during a kyphoplasty procedure (Kypho-IORT) were presented by Tina Reis (Mannheim/Germany). Updated clinical results comprised cohorts of a pilot phase (n= 52) and a recent dose escalation phase II study (n=9). Sixty-one patients received IORT with 50 kv Orthovolt x-rays. The tested dose escalation levels were 8 Gy in 8 mm, 8 Gy in 10 mm and 8 Gy in 13 mm depth from the isocentre of the radiation source, respectively. After three, six and twelve months, overall survival for all patients amounted to 76.9%, 64% and 48% and progression-free survival 97.5%, 93.8% and 93.8%, respectively. A significant pain reduction three, six and nine months after Kypho-IORT compared to pre-therapeutic baseline evaluation was achieved.

Further clinical results of IOERT during decompressing surgery of thyroid metastases to the spinal cord were presented by Katsuyuki Karasawa (Tokyo, Japan). In total, 48 patients were treated with a median dose of 20 Gy (range 16-26), while the region of the spinal cord was protected by lead shielding. In 29 patients additional EBRT was applied, mostly in a ▼

post-operative setting with median doses of 35.5 Gy (range 20-40). Median follow-up amounted to 33 months. In 15 out of 17 patients who were initially unable to walk, movement was restored. Overall median survival time was 38 months, three and five-year overall survival rates 51% and 33%, respectively.

In conclusion, Kypho-IORT with doses around 8 Gy at 13mm seemed to be a good treatment option for patient with spinal metastases in order to reduce pain as well as to ensure adequate tumour control. IOERT in combination with surgical intervention for metastases of the spinal cord was able to improve impaired neurological function.