versus 0.4%), and just fell within the pre-defined non-inferiority margin of 4.5%. However, in patients with low risk factors like suggested by the ESTRO or ASTRO consensus' criteria, there were not statistically different LLRs in both arms, and also in patients with luminal A molecular subtype the LLR was very low in the IORT arm, about 1%. It was also found that there was no significant difference in the 5-year overall survival rate in two arms, that is, 96.8% in the ELIOT arm and 96.9% in the EBRT arm. For patients with higher risk factors, a new strategy has been now developed, which include a hypofractionated WBI to be given after surgery and ELIOT. The TARGIT-A trial was a multicentric trial. The inclusion criteria were stricter than in the ELIOT trial. It included patients with unifocal small breast cancer with non-lobular histology and tested the concept of risk-adapted single-dose IORT, which was followed by external-beam WBI in patients with additional unfavorable risk factors. The latest published results from the TARGIT-A trial, with a median follow-up of 2 years and 4 months, reported a LRR with IORT of 3.3% and with EBRT of 1.3, meeting the non-inferiority margin of 2.5%, set at the outset. Overall, breast cancer mortality in the IORT arm was 2.6% versus 1.9% in the WBI arm. In addition, non-breast cancer deaths were found to be significantly reduced in the IORT arm: 1.4% versus 3.5%, with p = 0.0086. Toxicity and cosmesis were assessed by different methods in the studies, but in any case a favorable outcome has been shown. The comparison between the current standard or alternative PBI approaches for early stage breast cancer with data coming IORT techniques poses a dilemma as to when preliminary results are sufficiently mature to be allow practitioners and patients to consider a new treatment approach as safe. We know that most data from studies of breast conservation therapy have demonstrated the importance of long-term data (up to 20 years) in determining the ultimate efficacy of a treatment. The level 1 randomized evidence produced by the IORT trials show that this technique is very convenient for the patient, effective and has few side effects, rather than any postoperative treatment or procedures. Patients have every right to be offered an informed choice.

SP-0306
IMRT is the best for PBI
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Several clinically controlled randomized trials on accelerated partial breast irradiation (APBI) are currently being conducted and some of these have now published results. The trials have used different strategies, for example different patient selection criteria, doses and number of fractions, overall treatment time, treated volume and radiation techniques. Many trials have compared the APBI treatment to whole breast irradiation (WBI) 50 Gy/25 fr followed by a boost. External beam APBI is an attractive strategy, because every radiation department will be able to do the dose planning. The demand for technical skills is in principle not higher than for conventional dose planning. Few randomized trials have reported data, but unfortunately the largest one has not been promising.
In the phase III randomized RAPID trial significantly worse cosmetic outcome was reported with median follow up 36 months in 2135 patients randomized 1:1 to APBI based on 3D-CRT with 38.5 Gy/10 fractions, 5 days, versus WBI based on 42.5Gy/16 fr or 50Gy/25 fr +/-boost. Adverse cosmesis was higher in APBI-treated patients compared with WBI patients as assessed by trained nurses (29% vs 17%; p=0.001) and by patients (26% vs 18%; p=0.02). Grade 3 adverse events were seen in 1.4% of APBI patients, and not in WBI patients. With median 5 years follow up data from another phase III trial involving 520 patients randomized to APBI with IMRT using 30 Gy/5 fr versus WBI using 50 Gy/25 fr + boost has been reported by Livi and coworkers. Significantly better results were seen in APBI patients regarding acute (p=0.0001), late (p=0.004) and cosmetic morbidity (p=0.045). Local recurrence was seen in 1.5% of the patients. Thus data from large phase III trials supporting routine use of external beam APBI at the present time are not available. However, it is to be expected that the UK IMPORT LOW Trial will be able to report data from >2000 patients with median 5 years follow up at the Early Breast Cancer Conference (EBCC) March 2016. In that trial the strategy is based on 40 Gy/15 fr in all 3 arms, where arm 1 is WBI, arm 2 is partial breast irradiation, and arm 3 has a gradual dose using 40 Gy/15 fr to partial volume and 36 Gy/15 fr to residual breast. At EBCC, data on morbidity will also be reported from the DBCG PBI trial, which has included >800 patients and randomized them to APBI versus WBI using 40 Gy/15 fr in both arms. Data from these 2 trials will be presented and discussed at ESTRO 35. If the results from the IMPORT LOW Trial show that PBI using 40 Gy/15 fr is safe, and these data are supported by results from the DBCG PBI trial using the same treatment, then there is support for the statement that *IMRT is the best for PBI*. However, we are also awaiting results from the ongoing NSABP B-39/RTOG 0413 trial, which has accrued >4000 patients, who were randomized to APBI versus WBI. The majority of patients in the APBI arm have been treated with 3D-CRT. Many of the APBI trials were designed and initiated a decade ago, where the local recurrence risk was higher than we see today. Therefore some of these trials are underpowered to support the statement they are investigating. It is to be expected that results from several trials investigating external APBI will be published in the near future, and hopefully results from the trials will be included in meta-analyses to achieve enough statistical power to identify subgroups of patients where APBI is safe and other subgroups where WBI is to be preferred.

SP-0307
Dosimetric pros and cons of available PBI techniques
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Partial breast irradiation (PBI) can be performed with various techniques including both **brachytherapy (BT)** and **external beam radiotherapy (EBRT)**. These methods differ from each other regarding technical skill and dosimetric characteristics. Recent developments in imaging, dose calculation algorithms and beam delivery techniques have made all methods clinically feasible, but in most institutions the applied method mostly depends on the physician's preference and the technical availability.
Among all techniques the longest experience exists with **multicatheter interstitial BT** which can provide highly conformal dose distribution, large dose gradient at target edge, but it is quite complex and requires certain manual skilfulness. The possible geometric miss can result in significant under dosage of the target.
Technically, the **intracavitary applicators** are easier to be used and with balloon-type applicators no geometric miss can occur, but proper tissue conformance is not always guaranteed. In dosimetric point of view drawbacks of the Mammosite applicator are the spherical dose distribution, the symmetric margin and the potential high dose to skin, lungs and ribs. In some anatomical situation the balloon can be asymmetric resulting in asymmetric target coverage. The multichannel applicators are more flexible regarding shaping the dose distribution and reducing dose to critical structures without compromising the target volume coverage. With these applicators asymmetric margins can be used to a small degree.
In **intraoperative electronic BT** using spherical applicators the dose distribution is also spherical and a large dose inhomogeneity develops due to the sharp dose fall-off of the low energy X-ray beam. The margin is always symmetric, but the geometric accuracy is always ensured.
At **intraoperative irradiation with electron beams** there is no 3D-defined target volume, modulation possibilities to shape the dose distribution are very limited and conformal radiotherapy cannot be performed.
Linear accelerator based EBRT techniques expose relatively large volumes of non-target breast to high dose mainly due to the extended target volume created from CTV. In three-dimensional conformal radiotherapy (3D-CRT) dose to contralateral breast, lung or heart can be reduced with

proper selection of beam orientations. With intensity modulated radiotherapy (IMRT) highly conformal dose distribution can be achieved, but volumes irradiated by low doses can be larger than with 3D-CRT. Regarding the dose to OARs, with multicatheter BT the critical structures can be better spared than with 3D-CRT/IMRT except for the heart whose dose in BT is strongly dependent on the location of the PTV. With image guidance in EBRT the dose to OARs can be significantly reduced. At left sided lesion the dose to heart can be considerably decreased with deep inspiration breath-hold technique.

With special EBRT equipments such as **Cyberknife** or **Tomotherapy** which are equipped with image guidance smaller CTV-PTV margin can applied which reduces the dose to OARs while maintaining proper target coverage. Real-time tracking with Cyberknife can provide better target volume coverage and spare nearby critical organs, but the treatment time is too long.

Proton beam irradiation, due to the more favourable dose characteristics of proton beam, can provide the less dose to organs at risk, but the availability of the technique is sparse.

Symposium: New challenges in modelling dose-volume effects

SP-0308

Evaluating the impact of clinical uncertainties on TCP/NTCP models in brachytherapy

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During the past decade many investigations have been performed to investigate and minimize clinical uncertainties that could lead to significant deviations between the planned and the delivered doses in radiotherapy. Among the sources of uncertainties patient setup plays an important role in EBRT. Analogously, in brachytherapy the geometric uncertainties caused by movement or reconstruction uncertainties of the implant position in relation to the CTV and/or normal tissue can lead to systematic or random variations between prescribed and delivered dose. At the same time interfraction or intrafraction variations of the anatomy, e.g. caused by variations of position, shape and filling status of OARs, during the course of a treatment pose an additional challenge to all types of radiotherapy.

Recent investigations of different types of uncertainties for a variety of treatment sites, including gynaecological, prostate, head and neck, or breast BT, have led to numerous reports on accuracy of image guided brachytherapy. These have triggered the development of the recommendations for reporting uncertainties in terms of their dosimetric impact (GEC-ESTRO / AAPM guidelines, Kirisits et al. 2014, Radiother Oncol 110). Following these guidelines for uncertainty analysis, individual BT workflows can be analysed in order to identify those components of the overall uncertainty budget which will have the largest impact on the total delivered treatment dose. Once identified, strategies for reducing these uncertainties can be taken into consideration, such as repetitive/near treatment imaging, advanced online dose verification tools, etc.

In order to assess the clinical benefit of such uncertainty reduction measures, it is important to understand the interplay between different types of uncertainties and their combined effect on clinical outcome, in terms of TCP and NTCP. In the past, dose-response relationships have been derived from clinical data, which could not take into account the accuracy of the reported dose. For some treatment sites, e.g. for cervical cancer, uncertainty budgets and dose-response relations have been described in the literature in sufficient detail that now allows us to simulate what impact specific clinical uncertainties would have on TCP/NTCP modelling. In addition to that, one can simulate how TCP or NTCP models would change, if systematic and random dosimetric uncertainties could be reduced.

In this presentation a few such simulation examples will be shown to illustrate the clinical impact of uncertainties for source calibration, applicator reconstruction, interobserver variations and anatomical interfraction variations. Strategies for reducing clinical uncertainties will be discussed.

Finally, we will come one step closer to answering the questions whether reducing our clinical uncertainties is possible and meaningful, and if so, which strategies would have the largest clinical impact. In the future dose prescription may be affected by technological improvements that lead to a reduction of dosimetric uncertainties and a subsequent widening of the therapeutic window. These developments would benefit from a common effort in the BT community to investigate dose-response relationships for various treatment sites, and to simultaneously report uncertainty budgets for the underlying workflows applied for image guided brachytherapy, in our current clinical practice.

SP-0309

Incorporation of imaging-based features into predictive models of toxicity

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The probability of local tumor control is limited by the amount of dose deliverable to the tumor, which is limited by the amount of radiation induced toxicity. There is a large, and currently unpredictable, interpatient variation in the amount of observed toxicity. Since the expected patient specific toxicity is not known, the prescribed dose is restricted such that, within the patient population, the number of patients with major or even fatale toxicity is limited. Due to the interpatient variation in toxicity the population based dose limits lead to undertreatment of patients with low normal tissue irradiation sensitivity. This issue could be addressed if, on a patient specific level, it would be possible to classify the patients according to expected toxicity prior to or early during the treatment course – which calls for predictive models of toxicity.

Many clinical factors such as performance status, patient age, and other co-morbidity are associated with observed toxicity, and models based on such factors are today available (e.g. http://www.predictcancer.org/). The models can be a useful tool to optimize the treatment on the population level, but in order to be used on a patient specific level, input of more patient specific information is needed. During planning and delivery of radiotherapy a large number of patient images are acquired. The information content in the images is often reduced to a few figures (e.g. volume of tumor or measurement of patient positioning). The different types of images (CT/SPECT/PET/MR/CBCT) are available for free, and it is tempting to believe that these images could provide more patient specific information, if extracted in a proper way. Also as part of the response evaluation it is likely that imaging could be used to quantify the degree of toxicity. At the end of the day, the overall toxicity level can only be assessed by the patient, who should cope with the toxicity on a daily basis. However, in terms of biological tissue response to the radiation, patient (or oncologist) reported toxicity is likely to underestimate the “true” amount of toxicity since the toxicity effects might be overshadowed by treatment related gains e.g. re-ventilation of obstructed airways due to tumor regression in lung cancer patients, or because the toxicity is assumed to be related to co-morbidity. Disentanglement of such effects is desirable during creation of predictive models of toxicity; which might be feasible by evaluation of follow-up images.

The most used imaging-based feature to predict toxicity is obviously measurement of dose to individual risk organs (e.g. dose to heart or lung). These values are routinely used clinically and typical not regarded as image-based features. More advanced imaging-based features such as homogeneity, texture, or time changes of signals/images has been proposed