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ABSTRACT BOOKLET

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Targeted intraoperative radiotherapy (TARGIT IORT) during breast conserving surgery for early breast cancer in patient after breast augmentation with implants

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Background: Targeted intraoperative radiotherapy (TARGIT) has become a standard option during breast conserving surgery for selected cases of early breast cancer and over 20,000 patients have been treated in over 300 centres around the world. Although a growing number of patients are presenting with implants after breast augmentation, no data have been published yet regarding the safety of TARGIT with implants in situ. TARGIT IORT as a replacement of whole breast irradiation is an important issue in this context because of the high rates of capsular fibrosis following EBRT in such patients. **Methods:** We are reporting the outcome of a cohort of 11 patients from 5 centers, who received TARGIT during breast conserving surgery for early breast cancer, had undergone breast augmentation with implants before and wanted their implants to stay in situ. Patients were informed that no published data existed and decided for this approach on an individual basis. 3 patients received additional EBRT after TARGIT IORT because of presence of EIC or LVI.TARGIT IORT was performed using Intrabeam - 50 kV – X-rays delivering 20 Gy prescribed at the surface of the tumor bed during the initial lumpectomy procedure. **Results:** Follow-up varied from 76 months to 9 months. 10 patients presented with invasive breast cancer, 1 patient with DCIS. There were no procedure related complications. No breast cancer-related events or any events in any of the patients occurred to date and none have needed to have change of implant.**Conclusion:** This series of patients with TARGIT during breast conserving surgery for early breast cancer after breast augmentation with implants in situ revealed no safety concerns. Although limited by the small number of cases our results give some confidence in discussing this option with suitable patients. To expand this series, we are gathering details about other cases from the whole TARGIT group worldwide.

Comparison of Radical Dose IORT and EBRT the view of Local Recurrence and Complications According to Demographic, Pathologic and Biologic Factors in Early Breast Cancer.

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Hypothesis: The current standard treatment for early breast cancer includes conservative surgery followed by entire breast radiotherapy (RT). Recent study findings show that most local recurrences are in the scar tissue area suggesting that whole-breast RT may not always be necessary. If the volume of breast tissue to be irradiated is limited, RT may be performed intraoperatively. Intraoperative RT could in principle substitute the currently used radiation course of external RT after breast-conserving surgery in selected cases. **Patients and Methods** . We applied IORT to 224 patient with early breast cancer and suitable for breast conserving surgery. Suitable criteria was ; age > 45y,T < or = 3cm ,N=0 .Though we included some patients 40-44y and T= 3-4cm ,N=0 and favorable biomarkers as Possible Group .Afterwards, we compared results with control group. **Results** Patiens were enrolled at two center. Khatam Hospital patiens were delivered IORT during surgery and Azar Clinic patients received external RT after surgery. After four year local recurrence was 6(2%) in CaseGroup and 3(0.9%) in ControlGroup Mortality was 4 breast cancer related death and the other one, none breast death in ControlGroup.There was not any death in IORT patients. **Conclusions** Comparison of Local Recurrence in two groups (P value,0.078),demonstrated that IORT in contrast with EBRT had not inferiority.

Interim Update of the Targeted Intraoperative Radiotherapy United States (TARGIT-U.S.) Phase IV Registry Trial

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Background: Much of the evidence supporting targeted intraoperative radiotherapy (TARGIT) is derived from non-United States populations. Here we report the interim analysis of acute and chronic toxicity in a large cohort of U.S. women receiving TARGIT for early stage breast cancer. **Methods:** The TARGIT U.S. Registry trial is a pragmatic, prospective, non-randomized, multicenter registry trial. Women age 45 years and older with invasive ductal carcinoma were enrolled and received TARGIT at the time of breast conserving surgery. Whole breast external beam radiotherapy was also administered for women found to have unfavorable findings in their surgical pathology results, with TARGIT serving as the tumor bed boost. The primary objective of the study was to determine the rate of local recurrence. Secondary objectives included determination of treatment related acute and chronic toxicity and morbidity. Toxicity assessments were performed every six months after treatment for up to five years. **Results:** With median follow-up of 12.8 month (range 1 - 58), 657 patients were enrolled at 24 centers in the United States since May 29, 2012. 546 patients (83%) received TARGIT (20 Gy) at the time of breast conserving surgery. 111 patients (17%) received whole breast radiotherapy with TARGIT Boost due to unfavorable surgical pathology. Overall, 72.1% of patients identified as White, 5.7% as Asian, 10.5% as Black or African American, and 11.2% had unspecified race/ethnicity. Mean age was 66.4 years in the TARGIT group and 64.1 years in the TARGIT Boost group. More than 95% of patients were postmenopausal. Mean tumor size was 12.4 mm in the TARGIT group and 15.5 mm in the TARGIT Boost group. Negative margins were documented in 91% of patients in the TARGIT group and 69% of patients in the TARGIT Boost group. Patients in the TARGIT group were less likely to have high grade tumors (6.2% vs. 14.4%) or node-positive disease (8.1% vs. 36.9%). Seroma was the most commonly reported adverse event, but few seromas required radiologic or operative intervention (2.7% TARGIT vs 4.5% TARGIT Boost). Wound infection (3.2% vs. 4.5%) and hematoma (3.4% vs. 1.8%) were also infrequent in the TARGIT and TARGIT Boost groups, respectively. Delayed wound healing was reported in 1.3% of patients in the TARGIT group and 1.8% of patients in the TARGIT Boost group. Telangiectasias were not observed within the study. **Conclusion:** TARGIT is a safe method of delivering radiotherapy at the time of breast conserving surgery. Acute and chronic toxicity in this U.S.-based study is comparable to acute toxicity rates reported in the international TARGIT-A trial and other studies of partial breast radiation.

Breast conserving therapy and Intra-operative Radiotherapy – impact of the appropriate patient selection - a single-institutional long term analysis

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PURPOSE:Accelerated partial breast irradiation (APBI), including Intraoperative Radiotherapy (IORT), is a promising method of adjuvant treatment in breast conserving therapy. The appropriate patient selection is an important factor that influences local failures (LF) and the necessity of further irradiation post APBI. The literature suggests that the rates of LF after conservative treatment range from 1.1 to 4.2% after APBI as single adjuvant radiation modality and 0.5 to 2.5% for whole breast radiation (WBRT). **MATERIAL AND METHODS:**We retrospectively analyzed the influence the use of two published inclusion criteria (ASTRO and ESTRO) and the incidence of LF. All patients with biopsy proven invasive ductal carcinoma, pathological staged as pT1-2N0, irradiated with IORT (20Gy -single dose) at AC Camargo Cancer Center, Sao Paulo, Brazil, between 2005 and 2014 were included in the study. **RESULTS:**A total of 146 patients were treated IORT. The minimum follow up was 36 months (median – 62 months). From the total 55 (37.7%) and 97 (66.4%) patients met the ASTRO and ESTRO criteria, respectively. The crude LF rate was 3.4% (5/146 patients). When only patients in

accordance with the ASTRO and ESTRO criteria were included the LF rates dropped to 1.8% (1/55 patient) and 3.1% (3/97 patients). One of the patients who had LF could not be included in none of the criteria. **CONCLUSIONS:** an Institutional Protocol based on international guidelines can reduce the chance of LF post IORT selected patients.

Session 2 // Neuro

Local control and toxicity of IORT with low engery X-rays as adjuvant treatment after resection of brain metastasis - a retrospective analysis of patients treated at the Klinikum Augsburg

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Purpose and objectives: The paradigm of adjuvant radiotherapy after resection of brain metastasis is changing from whole brain irradiation (WBI) to localized brain radiotherapy (LBRT). Improving survival of stage IV patients, puts neurologic late toxicity more and more into focus. IORT with low energy is a promising method to apply LBRT for brain metastasis as it maximally shortens the resection radiation interval as well as the time to the start of mostly needed systemic treatment compared to external beam radiation.**Materials and methods:** We performed a retrospective analysis of patients treated with low energy X-ray IORT after resection of brain metastasis (4 colorectal cancer, 4 melanoma, 3 NSCLC, 2 renal cell carcinoma) between 2013 and 2017 at the Klinikum Augsburg. In total 19 metastasis in 17 patients (8 males/9 females) were resected and treated with IORT using the Intrabeam system. Four patients had recurrent disease, of which 3 were pretreated with WBI. All patients fitted to RPA class 1 and 2 (6 and 11 patients). Median age was 62,5 years (52-82 years), median applied dose 18Gy (16-20Gy) on the surface of the applicator and median applicator size 2,5 cm (1,5 -4cm). None of the patients received additional planned WBI. Actuarial overall survival (OS), local control rate (LC), distant brain control (DC) were calculated by the Kaplan-Meier method and put into context with published and own data of adjuvant LBRT with radiosurgery (SRS) or hypofractionated stereotactic radiotherapy (HSRT). **Results:** With a median follow up (FU) of 11 months, actuarial overall survival (OS) @ 1 year (2 years) was 69% (54%). The LC (actuarial LC @1year/@2years) of all 19 lesions was calculated 89% (84%/84%). DC of the 17 patients @1year (@2years) was 43% (43%). We found a symptomatic brain necrosis rate of 5% (1 lesion/ pre-treated with WBI+SRS boost), but found asymptomatic radiotherapy induced MR alterations also in the FU of 2 other patients (11%/cumulative 16%). One air embolism occurred during the IORT procedure. One patient developed a lethal infarction of the a. cerebri media 14 days post surgery. One patient with 2 consecutive resections and IORT procedures developed a bacterial meningoencephalitis. No other healing complications were observed. There was no increased use of steroids post operatively compared to patients with brain metastasis resection only. **Conclusions:** IORT with low energy is a feasible option to apply LBRT after resection of brain metastasis providing comparable local control with no increased toxicity compared to postoperative external beam LBRT. It provides the chance of earlier start of systemic treatment after resection of brain metastasis compared to external beam LBRT.

Session 3 // Breast II

Local recurrence patterns for locally advanced breast cancer treated with intraoperative radiotherapy boost after neoadjuvant chemotherapy

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Introduction: Locally advanced breast cancer patients, and in some cases early stage, previously were treated with radical mastectomy, however, since three decades ago neoadyuvant chemotherapy has become a standard treatment in the management of this patients, allowing in many cases, breast conserving surgeries. Radiotherapy is fundamental in the management of breast cancer, reducing local and loco-regional recurrence rate after breast conserving surgery. The development of radiobiological and technological understanding have brought upon the use of new radiation techniques, being intraoperative radiotherapy (RIO) one of them, allowing the radiation of the surgical bed with much more precision in real time during surgery, reducing the numbers of sessions of external radiotherapy, thus toxicity. **Method:** of 32 cases, we selected 29 patients, all women, with pathologic diagnosis of stage IIA and IIIB breast cancer, all receiving neoadyuvant chemotherapy before breast conserving surgery with RIO to the surgical bed as BOOST, between 2014 and 2016 in the National Institute of Neoplasic diseases. Two cases were excluded because of synchronic neoplasia and another one underwent mastectomy because of positive surgical margins. Descriptive analysis of the information was made and Kaplan-Meier method was used for global and local recurrence free survival curves. **Results:** of the 29 patients in the study, 1 pure local recurrence was reported (3.5%) and 2 mixed local recurrences (6.9%), one of them with distant progression and the other with axillary recurrence. None had local recurrence in the surgical bed, these were near the tumor bed. One of the patients had the recurrence reported before receiving complementary EBRT, the other two received 45 Gy. All the patients who reported recurrences were under 50 years of age, and none achieved a complete response with the neoadyuvant chemotherapy. A relationship couldn´t be stablished between the variables and the local recurrence because of the size of the events. One case of distant progression without local or regional recurrence was reported. The 24-month diseases free survival was estimated at 86.4% and the 12-month local recurrence free survival at 93.3% and 24-month at 89.7%. **Conclusions:** Intraoperative radiotherapy is a safe radiation technique to the surgical bed, as a BOOST, with local recurrence rates comparable to the ones reported with EBRT, with the advantage of decreasing the numbers of EBRT sessions. The age younger tan 50 years is a pattern of recurrence already stablished in breast cancer. In the neoadyuvant context, the partial pathological response could be a risk factor for local recurrence. In this group of patients it is recommended to complement the EBRT with doses biologically equivalent to 75Gy.

Breast conserving surgery in combination with intraoperative radiotherapy after previous external beam therapy: an option to avoid mastectomy

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Purpose: Mastectomy is the standard procedure in patients with in-breast tumor recurrence (IBTR) or breast cancer after irradiation of the chest due to Hodgkin's disease. In certain cases a second breast conserving surgery (BCS) in combination with intraoperative radiotherapy (IORT) is possible. To date, data concerning BCS in combination with IORT in preirradiated patients are limited. This is the first pooled analysis of this special indication with a mature follow-up of 5 years. **Methods:** Patients with IBTR after external beam radiotherapy (EBRT; treated in two centers) for breast cancer were included. Patients with previous EBRT including the breast tissue due to other diseases were also included. IORT was performed with the Intrabeam™-device using low kV X-rays. Clinical data including outcome for all patients and toxicity for a representative cohort (LENT-SOMA scales) were obtained. Statistical analyses were done including Kaplan–Meier estimates for local recurrence, distant metastasis and overall survival. **Results:** A total of 41 patients were identified (39 patients with IBTR,

2 with Hodgkin`s disease in previous medical history). Median follow-up was 58 months (range 4–170). No grade 3/4 acute toxicity occurred within 9 weeks. Local recurrence-free survival rate was 89.9% and overall survival was 82.7% at 5 years. Seven patients developed metastasis within the whole follow-up. **Conclusions:** BCS in combination with IORT in IBTR in pre-irradiated patients is a feasible method to avoid mastectomy with a low risk of side effects and an excellent local control and good overall survival.

Intra-Operative Radiation therapy in Early Stage Breast Cancer: A first for Africa

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Background: The shortage of radiotherapy services in low to middle income countries means that some patients requiring radiation may not receive it. The few available radiotherapy units are overburdened, resulting in delays to therapy or the need to shorten the treatment course. This compromises the provision of breast conservation. IORT may offer an innovative solution to these problems. In November 2017, our institution became the first in Africa to offer IORT to early breast cancer patients. **Methods:** We performed a retrospective review of the first cases of IORT in a multidisciplinary unit in Johannesburg, South Africa from its initiation in November 2017. Patient selection criteria was mainly based on the current American Society of Radiation Oncology (ASTRO) guidelines. Most patients who received IORT for early stage disease had a negative upfront sentinel lymph node biopsy, negating the need for EBRT. Patient characteristics, histology, the use of oncoplastic surgery and any early complications were recorded. **Results:** To date, 34 patients have received IORT. Fifteen patients elected to have IORT due to distance from a radiation centre, while the remainder selected IORT after being offered a choice between EBRT and IORT. The mean age of the patients was 60 years (pure range 44 - 84 years). Sixteen patients presented with left-sided tumours. The majority of the tumours were of ductal origin (n=28) and of the luminal A biological subtype (n=24), with a mean tumour size of 14,9mm. A single patient with locally advanced breast cancer (T4N2) opted for IORT as a boost in addition to planned EBRT. Twenty-six patients underwent wide local excision with mastopexy, while the remainder underwent either wide local excision with parenchymal flap (n=7) or locoregional flap (n=1). Few complications were observed at 6 weeks follow-up: 2 patients presented with localised areas of fat necrosis and another with a seroma in the wound bed. **Conclusion:** The early experience with IORT in Africa confirms viability in our setting, with a low complication rate and no detrimental effects on breast conservation surgery. IORT has been well accepted by our patients. Local recurrence data will be published in due course. Medical insurance, education and cost models still need to be addressed in the African setting.

Intraoperative Radiation Therapy in Early stage Breast Cancer: A First for Africa, Oncoplastic Experience

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Background: The shortage of radiotherapy services and distance to treatment in low to middle income countries means that some patients may elect to avoid breast conserving surgery. Available radiotherapy units are overburdened, and distance to machines results in delays to therapy need to shorten the treatment course, or patients electing mastectomy with reconstruction. This compromises the provision of breast conservation. IORT may offer an innovative solution to these problems. In November 2017, our institution became the first in Africa to offer IORT to early breast cancer patients. **Methods:** We performed a retrospective review of the first cases of IORT in a multidisciplinary unit in Johannesburg, South Africa from its initiation in November 2017. Patient selection criteria was mainly

based on the current American Society of Radiation Oncology (ASTRO) guidelines. Most patients who received IORT for early stage disease had a negative upfront sentinel lymph node biopsy, negating the need for EBRT. Patient characteristics, histology, the use of oncoplastic surgery and any early complications were recorded. All patients recived oncoplastic surgery post tumour excision. **Results:** To date, 34 patients have received IORT. Fifteen patients elected to have IORT due to distance from a radiation centre, while the remainder selected IORT after being offered a choice between EBRT and IORT. The mean age of the patients was 60 years (pure range 44 - 84 years). Sixteen patients presented with left-sided tumours. The majority of the tumours were of ductal origin (n=28) and of the luminal A biological subtype (n=24), with a mean tumour size of 14,9mm. A single patient with locally advanced breast cancer (T4N2) opted for IORT as a boost in addition to planned EBRT. Twenty-six patients underwent wide local excision with mastopexy, while the remainder underwent either wide local excision with parenchymal flap (n=7) or locoregional flap (n=1). Few complications were observed at 6 weeks follow-up: 2 patients presented with localised areas of fat necrosis and another with a seroma in the wound bed. **Conclusion:** Photographic record of the oncoplastic results were recorded with patient satisfaction documented. Lessons learnt included extended use of drains; ensuring the skin blood supply is viable with a roll eversion technique of the skin flaps. The early experience with IORT in Africa confirms viability in our setting, with a low complication rate and no detrimental effects on breast conservation surgery with the use of oncoplastic techniques. IORT has been well accepted by our patients. Local recurrence data will be published in due course. Medical insurance, education and cost models still need to be addressed in the African setting.

Session 4 // Physics & Biology

Post-operative Monte Carlo heterogeneous treatment planning for Intrabeam breast IORT using a pre-operative CT scan.

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Purpose: Most of the Intrabeam (Carl Zeiss) breasts IORT utilize the TARGIT prescription protocol of 20 Gy at the surface of the applicator in terms of dose to water and a Beam-On-Time calculation in homogenous water based on source dosimetric data historically measured by a large ion chamber. However, the recent V4.0 source calibration utilizing a smaller ionization chamber results in 16 – 28% higher dose rates at the surface of the applicators than the TARGIT calibration. The Radiance (GMV), a Monte Carlo based treatment planning system, enables heterogeneous dose calculations utilizing a CT scan of the patient. Combining the V4.0 source calibration with heterogeneous dose calculations results in treatment plans which present correct doses to the breast and other organs and tissues. **Materials and Methods:** Since intra-operative CT during breast surgery is hardly an option, patients receive a pre-operative CT scan immediately after needle localization, when a wire marking the center of the tumor is inserted. After the CT scan the patients have the lumpectomy and Intrabeam radiation using the TARGIT prescription. Following the radiation a treatment plan is created in Radiance using the pre-operative CT scan and V4.0 calibration, prescribing accordingly higher doses at the surface of the actual applicator used for the IORT. The applicator is centered at the wire marking the center of the tumor, replacing the tissue removed by the surgeon. For cases in which the patient received during the same surgery more than one Intrabeam treatment to the same breast, composite plans are created in an external system. **Results:** Despite the increased actual (non-TARGIT) prescription dose by 24 – 26% due to the V4.0 Intrabeam source calibration for applicators used, the actual dose to the breast tissue was found to be substantially lower than dose to water, since most of the breast tissue of the Intrabeam patient population is adipose tissue, as discussed in Task Group Report 186 of the American Association of Physicists in Medicine (AAPM). On the other hand, dose to the bone (ribs) in case the lumpectomy cavity is close to the chest wall is very high as expected for the low photon energy of the 50 KeV Intrabeam source. In simulated calculations placing a 2.5 cm diameter applicator very close to the rib, the maximum rib dose can reach 60. 6 Gy, which is over 200 % of the

prescription dose. **Conclusion:** Pre-operative CT and Radiance treatment planning enable post-operative treatment plans reporting breast IORT in terms of correct isodose distributions and dose-volume histograms as is customary in radiation oncology and enable the radiation oncologist to assess the doses to critical organs, like ribs or lung, using the accepted dose constraints. For lumpectomy cavities close to the chest wall radiation shields protecting the ribs from high radiation doses may be considered.

The induction of radiation-induced subcutaneous fibrosis after intraoperative radiotherapy in breast cancer patients associates with epigenetic dysregulation

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Purpose/Objective: Late normal-tissue reactions limit the dose of radiotherapy (RT) given to cancer patients and affects their quality of life. Thus, the identification of patients with a predisposition for severe side effects before starting RT is a prerequisite for personalized treatment. For the treatment of breast cancer patients, RT-induced subcutaneous fibrosis is of high relevance, especially after intraoperative radiotherapy (IORT) given as an early boost before whole-breast RT (>30% fibrosis). Since the molecular mechanisms of fibrosis are not well understood, it was tested whether epigenetic regulation might explain inter-individual differences in fibrosis risk after IORT boost and if fibrogenic pathways could be modulated using drugs that modify epigenetic marks. **Materials and Methods**: Patients were treated with surgery and TARGIT IORT (20 Gy of 50 kV X-rays from Intrabeam) followed by external beam RT to the whole breast (46-50 Gy, 2 Gy fractions). Early-passage fibroblast cultures were established from skin biopsies taken from the upper arm before treatment. Fibroblasts from 45 patients without and 30 with fibrosis were included. Genome-wide DNA methylation profiling was performed using Illumina 450K arrays on 24 patient samples (12 with and 12 without fibrosis) and differentially methylated regions (DMRs) were validated by EpiTYPER MassARRAY. A variety of molecular and cell biological assays were performed to characterize a diacylglycerol kinase alpha (DGKA) DMR. Epigenetic modulation of this DMR was investigated using BET-bromodomain inhibitors (JQ1, PFI-1). **Results:** An association with the fibrosis status was observed for 177 DMRs, 35 of which showed >10% methylation differences or ≥2 DMRs in one gene locus. Of these, the DGKA DMR was of special interest, as it was identified as an enhancer region. Reduced methylation of this DMR resulted in recruitment of the profibrotic transcription factor Early Growth Response 1 (EGR1) after radiation and promoted radiation-induced DGKA transcription in fibroblasts from patients who developed fibrosis after RT. Pharmacological inhibition or silencing of DGKA by siRNA resulted in a reduction of profibrotic cellular processes. The exposure of fibroblasts to BET-bromodomain inhibitors significantly reduced the bleomycin-induced increase in mRNA expression of DGKA down to baseline levels. Similar effects were observed for the fibrotic markers collagen I and α-smooth muscle actin. **Conclusion:** The present study shows that preexisting differences in the methylation status in the genome may affect the patient's susceptibility for developing fibrosis after RT. A number of DMRs were identified of which DGKA was functionally associated with profibrotic processes. In addition, a DGKA enhancer region could be modulated by epigenetic drug treatment. Interference with epigenetic patterns of fibrosis predisposition may provide novel preventive therapies that improve RT.

Influence of wound fluid from breast cancer patients treated and untreated with intra-operative radiotherapy (IORT) on tumor spheroid

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For better definition of cellular mechanism associated Intra-operative radiotherapy (IORT)-treated wound fluid effects on cell proliferation by regarding differences physiological and pathological status in vivo compare to in vitro, we design a study to investigate surgical wound fluid effects on its primary human breast tumor cell culture in 3-D microfluidic model. Since cell toxicity and proliferation of wound fluid from IORT treatment after breast-conserving surgery in two-dimensional cell culture have been illustrated different from three-dimensional condition, in our previous study we showed the two-dimensional cell culture of different cell lines (MCF7, SKBR3, MDA-MB231 and MCF10) treated with wound fluid extracted from electron and x-ray IORT which determined no significant different toxicity between IORT wound fluid from surgery without IORT. So in ongoing project we are collecting wound fluids from patients treated and untreated IORT and will be used on tumor spheroid which taken from patient in three-dimensional microfluidic devices. Cytotoxicity and molecular test will be assessed in 3D cell culture. This study will illustrate the truly respond of wound fluid from IORT in tumor spheroid in 3d culture different from wound fluid extracted from surgery without IORT.

Dosimetry for irradiation with Intrabeam in a solid-water tumour-bed phantom: Comparison of ionisation chamber calibrations, backscatter, and film dosimetry

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Purpose: Doses to water delivered by Intrabeam according to the Targit protocol are calculated based on measurements with an exposure-calibrated ionisation chamber using ICRU Report 19. However, recent protocols use ionisation chambers calibrated in Kerma or Water, and together with revised values of dosimetric factors, this may influence the RBE values for clonogenic inactivation of cells with this source. The purpose was to compare different ionisation chambers and calibrations, assess the influence of backscatter, and to validate doses determined by film dosimetry for use with cell irradiation. **Materials and Methods:** Three identical soft X-ray ionisation chambers (PTW 23342) were used. Air kerma calibrations were available for all three chambers, two had additional calibrations in water dose, and one an additional calibration in exposure. Film dosimetry was performed with GafChromic ebt3. Irradiation with 50 kV X-rays (Intrabeam) was performed using a 40mm spherical applicator fitting into a tumour-bed phantom made of Gammex 457 solid water. The ionization chambers fitted into a Gammex 457 plate of the same thickness (18mm). Backscatter was provided by 0-5 plates of RW3 solid water, each 1cm thick. All irradiations were performed twice. Monte Carlo (MC) modelling of the source and calibration setup was performed using Geant4. **Results:** Dose rates for irradiation in the solid-water plate without further backscatter yielded a coefficient of variation, CV=2.49%, i.e. within the tolerance of 3%. For two of the chambers, water doses calculated from the kerma values according to the IPEMB protocol using recent values of [μ/ro_]w,a (ratio of attenuation coefficients between water and air), and k_ch (the chamber factor), differed by < 0.6% from the water-dose calibrations. For the chamber supplied with the Intrabeam radiation source, the kerma-based dose to water was 8% higher than the water dose calculated from exposure using Targit/ICRU19, the major contribution to the difference coming from the chamber factor (k_ch=1.05). Adding backscatter increased the doses by < 2% suggesting that the tumour-bed phantom and the ionisation chamber casing together with the 18mm solid-water plate provided almost full backscatter in this geometry. This

was supported by 8-14% backscatter measured with film dosimetry for Intrabeam with a “flat applicator” delivering a slightly harder beam in a forward direction (no phantom). Furthermore, we found an effect of beam hardening on film calibrations. **Conclusions:** Physical doses to water are slightly higher than the values determined by the Targit protocol and thus the RBE=D_ref/D_50kV is expected to decrease by the inverse ratio. MC calculations are in progress to validate the chamber factor and the effect of backscatter and will be presented. Preliminary validation of RBE values for cell inactivation confirm an enhanced RBE > 1 for 50 kV X-rays in the tumour-bed phantom 8mm from the applicator surface.

Dose distribution of miniaturized linac used in intraoperative radiotherapy. Comparison with vendor

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PURPOSE/OBJECTIVE: To measure the dose distribution for Intrabeam XRS 4 (Zeiss) in water and to compare with data provided by the vendor, with and without the spherical applicators. Depth dose, lateral isotropy and transference function were examined. **MATERIAL/METHODS:** The Intrabeam XRS 4 (Zeiss) system is used in our institution for intraoperative radiotherapy. It is a miniaturized accelerator that emits low-energy X-rays (maximum 50 kV). It runs with its own software (version 2.2) and has its own set of spherical applicators. The diameters of these applicators are 1.5 cm, 2 cm, 2.5 cm, 3 cm, 3.5 cm, 4 cm, 4.5 cm and 5cm. It has its own water phantom for dose distribution measurements. A 0.005 cm3 Soft X-Ray Ionization Chamber 34013 (PTW) can be inserted in two positions, one for depth dose distribution measurements and the other for lateral dose distributions. The camera stays static in one of these positions while the radiation source moves in relation to the camera. There is a dial which measures this movement. In both inserts the camera is covered by a cap, so that the distance between the surface of this cap and the effective point of measurement is 1.614 mm according to the vendor.
- Depth dose distribution
Charge was measured along the vertical axis, every millimetre from 3 to 20 mm, and transformed into dose thanks to the calibration certificate of the chamber.
- Transference function
The transference function was measured for every spherical applicator. It is defined as the ratio between the dose in one point with the applicator, and the dose in the same point without the applicator. It depends of the applicator in use and the point in space where we measure.We measured this function in three points along the vertical axis, for every applicator: in contact with the applicator, at 1 cm distance and at 2 cm distance.
- Lateral isotropy
Charge was measured around the source, symmetrically, in for points: at 0º, 90º, 180º and 270º. This was repeated for every applicator, and without applicator. **RESULTS:** - Depth dose distribution
Maximum difference between measurements and data from vendor was 5% from 4 to 20 mm. In 3 mm we had a 7% difference.
- Transference function
Difference between measurements and data from vendor was within 4% in every case.
- Lateral isotropy
Compared with each other, differences in measurements around the source were within 5%.
CONCLUSION:
- Depth dose distribution
According to the vendor, measured depth dose at 20 mm must be within 5.3% compared to the data supplied by the vendor. Thus, we had a good agreement from 4 to 20 mm. Next to the source (3 mm) a higher difference was found; this is justified because of the steep dose gradient.
- Transference function
Transference function must be within 10% (calculated from the uncertainty of the depth dose

distribution) so measured data is in good agreement.
- Lateral isotropy
According to the vendor, lateral anisotropy can reach a difference of 5%. Measurements are in good agreement too.

Initial experience with navigated Intrabeam breast cases

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Purpose: Breast INTRABEAM IORT is being delivered with visual guidance and with no 3D treatment planning. This based on the idea that the procedure is pretty safe considering that the deep depth dose curve keep organs at risk (OAR) away from the radiation. The final position of the applicator with respect to the OAR and the dose volume delivered to them are not collected nor checked. **Material and Methods:** Radiance, GMV, Spain, is a TPS developed for IORT providing dose to medium. A navigation module within radiance to locate the applicator in the operating room has been developed. Two patients going into breast IORT were CT scanned with radiopaque marks around the breast. A preplan was prepared with radiance identifying the applicator size, position and orientation, contouring the regions of interest and the DVH based on the calculated dose volume. Just before the surgery, the patient position is registered with respect to the previous CT scan. The position of the applicator is collected and a new DVH is calculated and compared with respect to the preplan. Considering that most OAR are in the chest wall and, this part of the body is not manipulated during the surgery, the usage of the previous CT scan seems to be pretty representative. **Results:** For patient #1, which has larger breasts, planned applicator size was 40mm, final one was 50mm. The distance between applicator positions - navigated vs pre-plan- is approximately 10.97 mm. In the preplanning, almost 7% of the lung received at least 1Gy. In contrast, in the navigated planning, the DVH shows that almost 13% of the lung received at least 1Gy (40% greater). Differences of received dose in the ribs are not significant (from 2-3% to 4-5%). For patient #2, with smaller breasts, the planned applicator was also 40mm, final one was 50mm. The distance between both positions was 3.86mm. Due to the small differences between the applicator positions, both DVHs are almost equal. Volume of the lung or ribs that receive at least 1Gy was only slightly different in the navigated planning (a difference of 2-3%) **Conclusion:** We succeeded in applying a procedure for positioning the applicator with respect to the previous CT scan, which seems to generate a more realistic dose calculation. Implication of the surgeons on the preplan should allow better estimation of the surgical margins and then, of the applicator size. Largest breasts can potentially produce largest displacements of the applicator with respect to the chest wall, which can deal to a better protection of the OAR, if the applicator position can be located precisely and dose calculated with radiance. Smaller breast are subject to smaller displacements and then the preplan could be more representative, anticipating the dose delivery in the OAR, with a latter confirmation in the OR. All in all, navigation seems to be a good tool to support IORT planning but should be better investigated with more cases for a better evaluation.

Session 5 // Other applications

Combination of perioperative chemotherapy and intraoperative radiotherapy for the treatment of resectable intrahepatic cholangiocarcinoma

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Introduction. A new treatment method involving neoadjuvant hepatic chemoembolization 5 days prior to surgery combined with intraoperative radiotherapy (IORT) followed by adjuvant chemotherapy was established for patients with resectable intrahepatic cholangiocarcinoma (ICC). The aim of the present study was to assess the safety and efficacy of this treatment scheme. **Method.** Records of 24 patients with resectable ICC treated in Botkin Hospital between 2015-2017 were reviewed. In all cases was used perioperative chemoradiotherapy (PeriCRT). IORT was performed using Carl Zeiss Intrabeam PRS 500 system. After chemoembolization, resection stage, a single dose of 20 Gy IORT was delivered using 50-kV x-rays to a depth of 1 mm from the applicator surface. Afterward a histological examination and electron microscopy of irradiated resection margin were performed. **Results**. All 24 patients with ICC underwent gross total resection (R0) with lymphadenectomy. The estimated median survival was 20 month. Long-term survival was 80,1% (PeriCRT) for 3-year survival, respectively (p< 0,05, 95% CI). All treatment methods were well tolerated by all patients, with few adverse effects and no serious complications. There was no association between outcomes, variations in tumor characteristics, marker concentrations and therapeutic response. **Conclusions.** Good 3-year OS for resected ICC was achieved by using novel PeriCRT treatment method.

Phase I/II trial of surface kilovoltage bra chytherapy in ocular conjuntival carcinoma: Preliminary results

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Purpose: To determine the safety dose and toxicity profile of adjuvant kilovoltage brachytherapy in post resected ocular conjunctival carcinoma. **Materials and methods:** Between October 2014 and June 2017, at the National Institute of Neoplastic Diseases from Peru, 39 patients with squamous cell carcinoma of ocular conjunctiva, T1 - T3, resected, were selected to adjuvant treatment. The portable accelerator of 50 kV INTRABEAM® (Carl Zeiss Meditec) was used, previous local anesthesia and blocking of ocular muscles movement. The doses used were 18 Gy for patients with free margins and 22 Gy for positive edges, according to calculation of equivalent dose of 2Gy per fraction of 46 and 66 Gy respectively, assuming a tumoral α/β ratio of 8 Gy. The prescription was done to 2 mm depth. **Results:** The median age was 69 years, distributed evenly between both genders, with a median follow-up of 12 months. The surgical margins were 59% free and 41% committed, with no difference between the institutions where the surgery was performed (p = 0.069). The median of tumor size was 7 mm with 2 mm of invasion, 61.5% was T2 and 35.9% T1. The mean time between surgery and irradiation was 1.5 months, 23.1% of patients developed grade I toxicity of spontaneous resolution, without evidence of greater degree in any case. The dose had no statistical relationship with toxicity (p = 0.533). One-year disease-free survival was 96.7%. **Conclusions:** Kilovoltage surface brachytherapy is an applicable and reproducible tool in the treatment of squamous cell carcinoma of ocular conjunctiva. The administered doses are safe and well tolerated by patients with low levels of acute toxicity. Longer follow-up is needed to establish disease control rates and late toxicities.

IORT in unresectable pancreatic cancer combine treatment

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Introduction: A novel treatment method involving palliative regional chemoinfusion of tumor vessels 7 days prior to surgery combined with intraoperative radiotherapy (IORT) followed by palliative chemotherapy was established for patients with localy unresectable pancreatic cancer. The aim of the present study was to assess the safety and efficacy of this treatment method. **Methods:** Records of 113 patients with unresectable PDAC treated in Botkin Hospital between 2013-2017 were reviewed. In 18 cases was used perioperative chemoradiotherapy (PeriCRT). Chemoinfusion contains Gemcitabine in dose 1000 mg/m2. IORT was performed using Carl Zeiss Intrabeam PRS 500 system. After resection stage, a single dose of 20 Gy IORT boost was delivered using 50-kV x-rays to a depth of 5 mm from the applicator surface. **Results:** 18 patients with PDAC underwent surgical gastric and biliary bypass. The estimated median survival was 294 days. Long-term survival was 30,7% for 3-year survival, respectively. All treatment methods were well tolerated by all patients. Complications were estimated by Clavien-Dindo classification. **Conclusions:** Good 3-year OS for localy unresectable PDAC was achieved by using novel treatment method.