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Purpose: To compare the combined intracavitary/interstitial brachytherapy (IC/IS) with intracavitary brachytherapy alone (IC) in cervical cancer treated with definitive radio-chemotherapy and MRI guided adaptive brachytherapy (BT) within the EMBRACE study and the impact on target dose, OAR dose and late morbidity.
Methods and Materials: The EMBRACE database containing 1129 cervix cancer patients enrolled in the study with treatment completed before 09/2014 was used for this study. Patients having a MRI based parametrial infiltration status (PI) at time of BT (n = 999) were divided according to their PI status at first BT: no PI (456 patients), proximal PI (412 patients) and distal + pelvic wall PI (122 patients). Patients in each group were compared according to the use of IC or IC/IS during the course of their treatment, to dose in the HRCTV, OARs, and to late morbidity. T-test was performed on target and OAR doses (all EQD2 with α/ß of 10 and 3 Gy) and Chi-square test was performed on patients' characteristics variables. Univariate analysis of morbidity Grade 2 and more (G2≤) (rectum, bladder, bowel, vagina, overall morbidity) was performed with actuarial probabilities based on Kaplan-Meier statistics.
Results: The median follow up was 23 and 26 months for the IC/IS and IC group, respectively. IC/IS patients with proximal PI had significantly less G2≥ bladder (19% versus 28%, p = 0.014), bowel (10% versus 22%, p = 0.002) and overall morbidity (51% versus 68%, p = 0.003) at three years, but no difference in G2 ≥ rectal and vaginal morbidity. A significant dose decrease was found for bowel D2cm^3 in the IC/IS group in comparison to the IC group (61 ± 8 Gy versus 63 ± 10Gy) while the same mean dose (D90) to the HRCTV was given. Rectal and bladder D2cm^3 was not significantly different. Patients with distal or pelvic wall PI experienced less rectal (13% versus 46%, p = 0.001) and bowel (13% versus 40%, p = 0.054) morbidity G2≥ at three years in the IC/IS group in comparison to the IC group while bladder and vaginal toxicities were not significantly different. Patients in the IS/IC group received a significantly higher HR CTV D90 (87 ± 9 Gy versus 80 ± 13 Gy, p < 0.001).
Conclusions: These results demonstrate that regardless of the extent of PI, the dosimetric and clinical advantages of combined intracavitary/interstitial brachytherapy compared to intracavitary brachytherapy alone are substantial. IC/IS brachytherapy allows for a significantly higher HRCTV D90 (7Gy) in patients with distal and pelvic wall PI than IC brachytherapy while leading to less rectal and bowel morbidity. For patients with proximal PI, the use of IC/IS brachytherapy was associated with less bladder, bowel and overall morbidity while allowing for the same target dose. Potential biases induced by treatment related factors still have to be addressed in a multivariate analysis. A more systematic use of IC/IS brachytherapy in cervix cancer patients with PI is therefore recommended, especially for OAR sparing and for increase of dose to the HRCTV.

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CONCOMITANT HYPOFRACTIONATED IMRT BOOST FOR LOCALIZED HIGH-RISK PROSTATE CANCER: FIVE YEAR RESULTS OF A PROSPECTIVE TRIAL
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Purpose: To report on the five-year efficacy results of patients with localized high-risk prostate cancer treated with a concomitant hypofractionated IMRT boost (simultaneous integrated boost) along with adjuvant androgen deprivation therapy (ADT).
Methods and Materials: From 2004-2010, a prospective Phase I-II study was conducted in patients with any one or more of the following: T3 disease, PSA > 20 ng/mL, or Gleason score 8-10. A dose of 45 Gy in 25 fractions was delivered to the pelvic lymph nodes along with a concomitant IMRT boost of 22.5 Gy to the prostate, resulting in a total dose of 67.5 Gy in 25 fractions to the prostate over five weeks. Adjuvant ADT was to be delivered for two to three years. Biochemical failure was determined by the Phoenix definition. Univariate and multivariate analyses were performed to look for predictive factors. A post-treatment prostate biopsy was to be performed at five years to assess for pathologic local control.
Results: Two hundred and thirty patients were treated and followed for the primary five year efficacy endpoint. Patients not lost to follow up have a minimum follow up of five years. Median age of patients was 72 years. Sixty-seven percent had GS 8-10, 44% had PSA > 20 ng/mL, and 27% had T3 disease. The median duration of ADT was 30.4 months. 79% received at least 18 months of ADT. The median PSA nadir was 0.02 ng/mL. 92% achieved a testosterone nadir of < 0.7 nmol/L. Five year probability of testosterone recovery (> 1.7 nmol/L) was 53.9%. Five year biochemical control rate was 83.7%. Five year overall survival was 93.7%. PSA nadir < 0.5 ng/mL independently predicted for higher biochemical control (HR 0.014; p < 0.0001), while a PSA nadir < 0.1 ng/mL independently predicted for longer overall survival (HR 0.129; p = 0.0024). Starting ADT in an adjuvant fashion (versus neoadjuvant) independently predicted for higher biochemical control (HR 0.419; p = 0.0116). ADT for ≤ 12 months independently predicted for worse overall survival compared to ADT for > 24 months (HR 6.667; p = 0.014). Of the 45 patients who underwent a five year prostate biopsy, five (11.1%) had a positive result showing malignant cells with no radiation effect. The biochemical control and overall survival of patients who had a post-treatment biopsy were not different from those without a biopsy. Five year actuarial incidence of Grade ≥ 3 GI and GU toxicities were 1.9% and 7.2%, respectively.
Conclusions: A concomitant hypofractionated IMRT boost delivering 67.5 Gy in 25 fractions to the prostate over five weeks combined with elective pelvic nodal irradiation and adjuvant ADT resulted in favourable five year biochemical control and overall survival rates for patients with localized high-risk prostate cancer. Lower PSA nadir predicted for higher biochemical control and longer overall survival. ADT duration of ≤ 12 months was associated with decreased overall survival. Pathologic local failure rate as assessed by five-year post-treatment biopsy was low.

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PROGNOSTIC VALUE OF PRE-TREATMENT SERUM LACTATE DEHYDROGENASE IN HPV-RELATED AND HPV-UNRELATED OROPHARYNGEAL CANCER
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Purpose: Serum LDH level is incorporated in the stage classifications of lymphoma, melanoma, and seminoma. Recent series have also shown it to be prognostic for nasopharyngeal cancer. We evaluated the prognostic value of pre-radiotherapy (pre-RT) LDH in HPV-related (HPV+) and unrelated (HPV–) non-metastatic oropharyngeal cancer (OPC).
Methods and Materials: All newly diagnosed p16-confirmed HPV+ and HPV– OPC patients receiving IMRT +/- chemotherapy from 2005-2013 were reviewed. Pre-RT LDH level was recorded as a binary variable [elevated (E) versus non-elevated (NE)]. Overall survival (OS) and relapse-free survival (RFS) were compared between LDH E versus NE by HPV status. Multivariable analyses (MVA) assessed the prognostic value of LDH on OS and RFS overall and in the subset with normal liver function (by AST/ALT/ALP). Recursive partitioning analysis (RPA) created prognostic groups in HPV+ OPC combining TNM and LDH.

Results: Of 939/1077 (87%) HPV tested OPC, LDH level was available in 611/678 (90%) HPV+ and 225/261 (86%) HPV–. Median follow up was 4.4 and 4.1 years for the HPV+ and HPV– cohorts, respectively. Among HPV+, LDH E (n = 223) versus NE (n = 388) cases comprised older age (median 60 versus 58 years, p = 0.02) and slightly larger primary tumour volume (GTV) (median 24 versus 21 cc, p = 0.08) but similar T (p = 0.27) and N-category (p=0.34), smoking pack-years (sPY) (p = 0.27), and alcohol consumption (p = 0.25). A lower three-year OS (79% versus 87%, p < 0.01) and RFS (79% versus 89%, p < 0.01) were found in HPV+ LDH E versus NE. MVA for HPV+ patients confirmed that LDH-E increased risk of death [HR 1.5 (1.1-2.2), p = 0.03] and relapse [HR 1.8 (1.2-2.7), p < 0.01) after adjusting for sPY (OS: p < 0.01; RFS: p = 0.94), age (OS: p = 0.09; RFS: p = 0.63), T3-4 (OS: p = 0.02; RFS: p = 0.48), N2c-3 (OS: p = 0.08; RFS: p < 0.01), GTV-1° (OS: p < 0.01; RFS: p < 0.01) and chemotherapy (OS: p < 0.01; RFS: p = 0.02). The prognostic significance of LDH-E was confirmed by MVA within the subset of HPV+ patients with normal liver function [OS: HR 1.7 (1.1-2.7), p = 0.01; RFS: 2.0 (1.3-3.3), p < 0.01]. RPA divided HPV+ OPC into low-risk (T1-3N0-N2c_LDH-NE) and high-risk (T4 or N3 or T1-3N0-N2c_LDH-E) subgroups. The three-year OS was 91% versus 72% and RFS was 91% versus 75%, respectively (both p < 0.01). In the HPV– cohort, no differences were found in baseline characteristics or outcomes between LDH E (n = 86) and NE (n = 139) cases (three-year OS: 59% versus 52%, p = 0.96; RFS: 68% versus 68%, p = 0.91), and the non-prognostic effect was confirmed by MVA (OS: HR 1.2, p = 0.43; RFS: HR 1.1, p = 0.54)

Conclusions: This study shows that pre-RT serum LDH elevation is prognostic for HPV+ OPC independent of liver function but non-prognostic for HPV– patients. LDH has the potential to be included in HPV+ prognostic groupings, similar to other tumours. T1-3N0-N2c HPV+ OPC with elevated LDH appears associated with increased risk of death and disease relapse comparable to T4 or N3 subsets

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A PHASE III RANDOMIZED CONTROL TRIAL COMPARING SKIN SPARING HELICAL TOMOTHERAPY TO 3D-CONFORMAL RADIOTHERAPY FOR ADJUVANT RADIOTHERAPY OF EARLY STAGE BREAST CANCER

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Purpose: Breast-conserving surgery followed by adjuvant radiation therapy (RT) is the standard treatment for early-stage breast cancer (EBC). Up to 30% of patients experienced moist desquamation or ≥ Grade 2 skin toxicity following standard fractionation tangent field 3D-conformal radiotherapy (3D-CRT). The feasibility of skin-sparing helical tomotherapy (SSHT) by configuring skin as an organ at risk (OAR) was established in an earlier dosimetric study. The aim of this study was to assess whether SSHT would reduce the incidence of ≥Grade 3 acute skin toxicity in EBC patients undergoing RT.

Methods and Materials: This single institution Phase III randomized control trial comparing SSHT to 3D-CRT for RT in EBC patients with acute skin toxicity as the primary endpoint. The skin as OAR was defined as a 5 mm strip of ipsilateral breast skin and we employed a constraint on the skin volume receiving dose up to 40 Gy while delivering dynamic IMRT as described earlier. Patients were assessed weekly during RT and then at six and 12 weeks post-RT. Acute toxicity parameters recorded were level of skin erythema, radiation dermatitis, and pain.

Results: During the period of May 2008 to January 2012, 177 EBC patients were enrolled into the study and 90 were randomized to 3D-CRT arm and 87 to SSHT. The mean age was 59 years. SSHT achieved more homogenous coverage of the target than 3D-CRT. HT arm had lower proportion of acute toxicity. The incidence of erythema and moist desquamation were significantly higher in the 3D-CRT arm than in the SSHT treated arm (erythema: 60% versus 39%; p = 0.005; moist desquamation: 33% versus 11%; P=0.0003). No patients in the SSHT arm had exudate while 11% of patients in the 3D-CRT arm did (0% versus 11%; p = 0.0014). Patients in the 3D-CRT arm had increased incidence of ≥ Grade 3 tenderness and discomfort of breast (tenderness: 54% versus 24%; p < 0.0001, discomfort: 9% versus 1%; p = 0.019), but ≥ Grade 3 itching, burning and pulling were not significantly different between the treatment arms. The independent prognostic factors that contributed significantly to acute toxicity in the multivariate analysis were large breast volume, adjuvant chemotherapy, and 3D-CRT.

Conclusions: SSHT significantly reduced the incidence of moist desquamation compared with 3D-CRT. Incidence of acute toxicity was correlated with large breast volume, adjuvant chemotherapy, and 3D-CRT. Combining an IMRT approach with explicit reduction in skin dose may further improve both acute and late skin toxicity for patients undergoing adjuvant breast radiotherapy.

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Abstract withdrawn

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THE ROLE OF STEREOTACTIC BODY RADIATION THERAPY (SBRT) IN GYNECOLOGICAL CANCERS: A SYSTEMATIC REVIEW

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Purpose: SBRT is an effective treatment that delivers highly conformal doses of radiation to target volumes, sparing normal organs. Despite the advancements in this technique for other disease sites, its role in gynecological cancers remains unclear. This systematic review aims to evaluate toxicity and outcomes of SBRT in gynecological malignancies.

Methods and Materials: In accordance to PRISMA guidelines, a systematic review of the literature was conducted on studies reporting SBRT in gynecological malignancies. EMBASE, MEDLINE and Cochrane databases were systematically searched for relevant studies until October 2015. All relevant studies evaluating the role of local-regional SBRT for gynecological malignancies (excluding CNS, extra-pelvic and extra-para-aortic lesions) were included. Relevant data regarding toxicities and outcomes were abstracted and analyzed.

Results: From 534 references, 23 articles from 2004 to 2015 were selected, comprising a total of 382 patients. Studies were classified into six categories: 1) Radical treatment with SBRT as local boost for cervix tumours: total of 34 patients were identified in seven studies. Treated PTV median volume (MV) ranged from 41 to 146 mL and local control (LC) from 0 to 100% in a median follow up time of 4 to 22 months. Gastro-intestinal (GI) G3/4 toxicity was ~12%. 2) Radical treatment with SBRT as a local boost for endometrial cancer: 13 patients found in three studies. Eighty-five percent of the patients were from one series reporting a 55% LC at 18 months. G3 GI toxicity was reported in one out of 13 patients. 3) SBRT to lymph node metastases: 197 patients were found in seven studies. Treated PTV-MV ranged from 16 to 42 mL and LC 60-100% in a range of median follow up time of 14-20 months. Long-term G3/4 GI and genito-urinary (GU) toxicity was 3% and 0.005%, respectively. 4) Pelvic recurrences treated with SBRT: Majority received a course of radiotherapy before, either as a previous treatment or as first course on salvage attempt. Seventy-two patients were found in 10 studies. Treated PTV-MV ranged from 20 to 154 mL and LC from 51% to 100% in a median follow up range of 4-22 months. Chronic G3/4 GI and GU toxicity were 22% and 1.5%, respectively. 5) Adjuvant treatment with SBRT to the vaginal vault after EBRT: 61 patients were found in three studies. LC was 91-92% (1-11 years) and GI G3 toxicity was 3%. 6) Two studies included two