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Risk of metachronous contralateral testicular cancer (CTC) among 3,745 Dutch men diagnosed during 1965–1995

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Background: Testicular cancer patients remain at risk of developing a CTC. It is still unclear whether treatment for the primary cancer, especially chemotherapy, alters the risk of developing a CTC. The aim of this study was to assess the risk of developing CTC with emphasis on the role of prior chemotherapy (CT).
Materials and Methods: In a nationwide cohort comprising 3,745 testicular cancer patients treated in the Netherlands during 1965–1995, covering 48% of all Dutch patients in this period, standardized incidence ratios and cumulative incidence of metachronous CTC were calculated. Seminomas and non-seminomas were analysed separately. Risk factors for developing metachronous CTC were assessed using multivariable Cox analysis adjusted for competing risks.
Results: The cohort comprised 1,716 seminoma and 2,029 (54.2%) non-seminoma tumors. While the majority of seminoma patients (84.9%) received RT, most non-seminoma patients received CT (54.2%) or surgery alone (28.8%). After a median follow-up of 14.1 years (inter quartile range 7.5–21.1 years) 80 CTC were diagnosed, 9 within 6 months of the primary tumor (synchronous CTC) and 71 thereafter (metachronous CTC). Of these metachronous CTC 63.4% occurred within 10 years. The SIR for all metachronous CTC was 23.6 (95% Confidence Interval (95% CI) 18.4–29.9), the SIR was 33.4 following a seminoma and 17.7 after a non-seminoma testis tumor ($p = 0.007$). The SIR more than halved for patients diagnosed after 1975 compared to patients diagnosed during 1965–1975 (48.2 versus 19.2, $p = 0.001$). The SIRS remained significantly elevated up to 25 years after diagnosis, the SIR was 21.8 for 0.5–10, 29.1 for 10–20 and 23.7 for 20–25 years after diagnosis. The 10- and 20-year cumulative incidence for metachronous CTC was 1.3% (95% CI 0.9–1.8%) and 2.3% (95% CI 1.8–3.0%), respectively. In multivariate analysis histology of the index tumor was not associated with metachronous CTC risk ($p = 0.464$). Metachronous CTC risk decreased with older age for seminomas (HR 0.35, $p = 0.001$) but not for non-seminomas ($p = 0.220$). Preliminary data suggest that CT reduces CTC risk. The results of multivariate analysis of treatment associated risks will be presented at ECCO.
Conclusions: The risk of CTC remains elevated for at least 25 years after the diagnosis of testicular cancer. However, the cumulative CTC incidence is low reaching 2.3% after 20 years of follow-up. CTC risk decreased markedly after the introduction of cisplatin containing CT regimens.

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Updated results of the BC2001 phase III randomized trial of standard vs reduced high dose volume radiotherapy for muscle invasive bladder cancer (ISCRTN:68324339): tumour control, toxicity and quality of life

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Background: Radiotherapy (RT) is an alternative to radical cystectomy in the management of muscle invasive bladder cancer. Limitations are probability of attaining and maintaining local tumour control and risk of late bladder toxicity. BC2001 tests whether concomitant chemotherapy (CT) improves loco-regional control and whether RT volume modification reduces late toxicity without detriment to tumour control.
Methods: Patients with T2/3 bladder cancer were randomized in a 2×2 factorial design to: i) RT vs RT + concomitant CT (5FU 500 mg/m^2 d1–5 wks 1 & 4 + mitomycin C 12 mg/m^2 d1), and/or(ii) standard RT to tumour and whole bladder with 1.5 cm margin (sRT) vs reduced high dose volume RT (RVRT) where tumour + 1.5 cm margin was treated to 100 ($\pm$5)% target dose and remaining bladder received 80% target dose. RT dose was 55 Gy/20F or 64 Gy/32F according to local practice. RT volume comparison results (primary endpoint RTOG toxicity at 1 yr) are reported. Target sample size was 480 pts but the RT randomisation closed early due to slow recruitment. Estimated power is 73% (two-sided $\alpha = 0.05$) to detect a 20% difference in G3/4 toxicity.
Results: 219 pts were recruited (108 sRT; 111 RVRT); 49 received neoadjuvant CT; 31 sRT and 33 RVRT were randomised to concomitant CT. Median age was 74 yrs. Median follow up is 37.5 months. There was no difference in loco-regional disease-free survival (LRDFS: HR = 0.96, 95% CI: 0.56–1.63)nor overall survival (HR = 0.88, (0.61–1.28)) between randomised RT groups. 2yr LRDFS is 72% sRT, 74%RVRT. 28(16) sRT vs 27 (15) RVRT pts have had local (invasive) recurrences ($p = 0.95$); 32 pts have undergone salvage cystectomy. No difference was seen in CTC G3/4 acute toxicity (26% sRT vs 21% RVRT, $p = 0.33$), RTOG G3/4 toxicity at 12 mths (9% sRT vs 4% RVRT, $p = 0.27$) nor Lent Som G3/4 toxicity at 12 mths (45% sRT vs 34%RVRT, $p = 0.21$). Bladder capacity fell significantly in sRT group (mean reduction at 12 mths: 59 mls, 95% CI: 2.5–117 mls, $p = 0.02$) but not in RVRT group (26 mls: −66 to 119 mls).
Conclusions: RT in the modern era can attain local control in most patients with T2-T3 bladder cancer. Acute and late toxicity was less than anticipated in both treatment groups. Modifying standard RT volumes had minimal effect on local control and toxicity in this trial. Two year toxicity and quality life data is currently under analysis and will be presented at the meeting

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Baseline and on-treatment expression of HIF-1a, HIF-2a and CAIX in patients with metastatic renal cell carcinoma

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Background: Protein-expression of Hypoxia Inducible Factor-1 (HIF-1α) and Carbonic anhydrase IX (CAIX) have both proven prognostic for overall survival in patients with clear cell renal cell carcinoma (ccRCC), whereas the prognostic role of Hypoxia Inducible Factor-2 (HIF-2α) remains unknown.
Material and Methods: We assessed HIF-1α, HIF-2α and CAIX in patients with metastatic ccRCC at baseline and during IL-2 based therapy. A pre-treatment tumour biopsy was available in 61 patients and among those 41 had an on-treatment biopsy. HIF-1α, HIF-2α and CAIX were evaluated by immunohistochemistry and correlated mutually and with overall survival.
Results: Positive HIF-2α staining was observed in both cytoplasm and nuclei, whereas HIF-1α was located predominantly in the nuclei. Forty-four (72%) of the tumours had positive cytoplasmic HIF-2α staining, and 26 tumours (43%) had nuclear HIF-2α staining. There was a significant positive correlation between nuclear HIF-2α and cytoplasmic HIF-2α, HIF-1α and CAIX ($p < 0.05$ in all comparisons), but no significant correlation between cytoplasmic HIF-2α and CAIX. The presence of baseline cytoplasmic HIF-2α was associated with favourable overall survival ($p = 0.01$), in contrast to nuclear HIF-2α, HIF-1α and CAIX. The association of cytoplasmic HIF-2α with survival remained significant in a multivariate analysis including MSKCC criteria and Fuhrman grade (HR: 2.4; CI 1.3–4.4; $p = 0.005$). Nuclear HIF-2α and HIF-1α expression changed significantly following IL-2 treatment ($p = 0.04$ and $p = 0.007$, respectively), with up-regulation of HIF-1α during treatment being associated with poor outcome (RR = 1.3).
Conclusion: This is the first study assessing HIF-2α expression in metastatic ccRCC indicating that cytoplasmic HIF-2α may be a favourable prognostic factor for overall survival. A large variability and heterogeneity in the expression of HIF-1α, HIF-2α and CAIX was observed.