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Oncologist case load volume and disease outcomes after definitive external beam radiotherapy for localized prostate cancer

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Purpose: To verify the 2007 Jeldres study (European Urology, 2007) which showed that low radiation oncologist (RO) case load volume (CLV) predicted worse outcome for definitive external beam radiotherapy (EBRT) of localized prostate cancer.
Methods and Materials: Our cohort comprises all men diagnosed with localized prostate cancer and treated with definitive EBRT by 30 radiation oncologists between 1998 and 2004. Data was extracted from the Provincial tumour and radiation registries with supplemental data from the Provincial pharmacy. The primary endpoint was the actuarial time to salvage therapy, categorized as above or below a provider volume of 10 annual or 120 cumulative cases. These low cut-offs were representative of the Jeldres trial design. Salvage therapy was defined as the first administration of androgen deprivation therapy (ADT) after EBRT, excepting adjuvant ADT. Median CLV was analyzed by provider volume quartile. Multivariate analysis (MVA) was performed for a subset of patients with full data (age, iPSA, Gleason score, stage, ADT duration, EBRT dose and treatment year). Secondary exploratory analysis of 5, 10, 20, 40 and 100 cumulative cases were examined for EBRT learning curve effects.
Results: 4982 men were treated in the 6 year accrual period. Median follow-up was 6 years. A CLV of $\leqslant$10 annual and $\leqslant$120 cumulative cases was significantly associated with a shorter time to salvage ADT ($p = 0.037$). On a subset of 676 men with full data available, MVA showed iPSA ($p = 0.003$), Gleason score ($p = 0.002$), ADT duration ($p = 0.028$) and EBRT dose ($p = 0.001$) were significant predictors, while CLV was not ($p = 0.068$). A learning curve was apparent at a threshold of 40 cumulative cases ($p = 0.048$), but not at higher or lower numbers.
Conclusions: Salvage ADT rates are significantly associated with a CLV of $\leqslant$10 annual or $\leqslant$120 cumulative cases. A trend towards significance was seen when accounting for competing prognostic factors, suggesting that EBRT should be delivered by high volume RO to achieve lower rates of salvage ADT and better biochemical outcomes.

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Further analysis of a Phase II randomized controlled trial (RCT) of a poxviral-based PSA targeted immunotherapy in metastatic castration-resistant prostate cancer (mCRPC)

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Background: Therapeutic poxviral vaccines for prostate cancer are safe with preliminary evidence of clinical benefit in Phase I/II studies. PROSTVAC-VF (PV) comprises 2 recombinant viral vectors, (Vaccinia and Fowlpox), each encoding transgenes for prostate specific antigen (PSA) and 3 immune costimulatory molecules (B7.1, ICAM-1, and LFA3: TRICOM). PV is administered subcutaneously in a heterologous prime-boost regimen with concurrent low-dose GM-CSF.
Methods: 122 patients (pts) were treated in a multi-center, double-blind, RCT of a vaccination series. Pts were randomized 2:1 to PV + GM-CSF vs. placebo empty vector + control saline injections (C). Vaccinia-based vector was used for priming followed by 6 planned Fowlpox-based vector boosts. The trial completed enrollment in July 2005. Eligible pts had metastatic disease (positive bone scan or lymph node enlargement by CT scan), a rising PSA despite castrate testosterone levels, and a Gleason score of $\leqslant$7. Pts with a history of prior chemotherapy use, visceral metastasis, or narcotic use were excluded. The 1° endpoint was progression free survival (PFS), with progression defined as 2 new lesions on bone scan or RECIST-defined progression. Vaccination was discontinued after progression.
Results: 82 pts received PV and 40 received C. Pt characteristics were similar and were favorable. Halabi predicted survival approximately 20−21 months. PFS was similar in the 2 groups ($P = 0.56$). However, at 3 years post study, PV patients had a more favorable overall survival outcome than C patients (25 alive, 30%, PV, versus 7 alive, 17%, C): longer median survival by 8.5 months (24.5 months PV, versus 16 months C); estimated hazard ratio 0.6 (95% CI 0.4−0.9); stratified log rank $P = 0.01$. Subset analysis reveals trends for improved vaccine effect in patients with above median LDH, and bone scan lesion number. However, both subsets, above and below medians benefited from treatment. Importantly, the subset of patients that had the greatest differential therapeutic vaccine effect was the HLA-A2 positive subset (Hazard ratio: HLA-A2pos PV/C 0.48 vs. HLA-A2neg PV/C 0.88).
Conclusions: In a randomized controlled trial, PV immunotherapy was associated with a 40% reduction in the death rate and an 8.5 month improvement in median OS in men with mCRPC. These data provide evidence of prolonged anti-tumor activity, but need to be confirmed in a larger Phase III study.

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A double blind, randomised, dose finding, phase II, multicentre study of radium-223 for the treatment of patients with metastatic castration-refractory prostate cancer (CRPC): EudraCT number: 2005−003680−22

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Background: Alpharadin® (radium-223) is a bone-seeking alpha emitting radioisotope now in phase III development for the treatment of CRPC. In contrast to older pain palliating radioisotopes used in CRPC, Alpharadin®is a new generation α-emitter, and the very short range, high-energy α-radiation may provide efficacy while sparing the bone marrow. The main objective of the study was to compare the prostate specific antigen (PSA) response rate of three different repeat doses of Alpharadin® in patients with CRPC and bone metastases. Secondary objectives included study of the effect of dose on changes in PSA, bone-specific alkaline phosphatase (b-ALP) and toxicity.
Materials and Methods: Patients had CRPC with bone metastases and without visceral disease, a castrate testosterone, Eastern Cooperative Oncology Group (ECOG) performance status 0−2, and PSA progression according to the PSA Working Group criteria. They were randomised to one of three Alpharadin® dose groups: 25, 50 or 80 kBq/kg, given once every 6 weeks for 3 cycles. The planned sample size was 117. The main outcome was PSA response (defined as a 50% decline confirmed $\geqslant$19 days later), with censoring at the time of new CRPC treatment or anti-androgen withdrawal. The study was done in 21 centres from 2006−8.
Results: 121 eligible patients, median age 70 years, median baseline PSA 127.6 ng/ml, were analyzed by intention-to treat. Thirty-seven (31%) had received prior chemotherapy. 107 (88%) received all 3 Alpharadin® treatments over 12 weeks. Confirmed PSA response was seen in 0%, 6% and 13% in the 25, 50 and 80 kBq/kg groups, respectively ($p = 0.0297$ test for trend). The median change in PSA at week 16 was 71%, 42% and 24%, respectively ($p = 0.050$), and in b-ALP was −34%, −58% and −61% ($p < 0.0001$). Alpharadin® was well tolerated. No patients stopped study treatment for toxicity. The most common adverse events were G-I and musculo-skeletal, with no evidence of a dose-effect. Grade 3 or 4 neutropenia was not seen. Grade 3 or 4 thrombocytopenia occurred in 2 patients, one from each of the 2 lower dose groups.
Conclusions: The study met the primary endpoint, showing a dose response for % PSA responders. In addition to the biochemical evidence of efficacy, Alpharadin® had a highly favourable toxicity profile. The results support the dose schedule used in the ongoing ALSYMPCA phase III trial, 50 kBq/kg every 4 weeks for 6 cycles.
Trial sponsor: Algeta