Podium Session 1: Prostate Cancer
June 23, 2013, 0810-0910

POD-01.01

A Competing-risks Analysis of Survival After Alternative Treatment Modalities for Locally Advanced Prostate Cancer Patients: A U.S. Population-based Assessment

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Introduction and Objectives: The efficacy of treatment with curative intent in patients with locally advanced prostate cancer (aPCA) is a subject of continuous debate. We tested the impact of initial treatment type (radical prostatectomy [RP], radiotherapy, hormonal therapy [HT] and observation) on cancer-specific (CSM) and other-cause mortality (OCM).

Methods: We focused on 3910 patients with clinically T3-T4 PCa, within the Surveillance, Epidemiology, and End Results-Medicare linked database. Patients were stratified according to treatment type, and either Gleason score or age categories. Competing-risks survival plots and regression analyses were used to estimate the impact of treatment type on CSM and OCM rates.

Results: At 10 years, CSM and OCM rates were respectively 14 and 28% in RP patients vs. 20 and 38% in radiotherapy patients vs. 36 and 47% in HT patients vs. 26 and 49% in observation patients (all $p \leq 0.001$). The same trend was observed when patients were stratified according to Gleason score or age groups. In the multivariable competing-risks analyses, the adjusted hazard ratios recorded for RP, radiotherapy, and HT were respectively 0.51 (95% CI: 0.36-0.72), 0.80 (95% CI: 0.65-0.99), and 1.28 (95% CI: 1.05-1.56) relative to observation (all $p \leq 0.04$).

Conclusions: Our results indicate that patients with locally aPCA should be considered for treatment options with curative intent (RP or radiotherapy), whenever feasible, regardless of tumour characteristics or patients age. With respect to treatment type, RP appears to provide the most favourable CSM rates.

POD-01.02

The Significance of Finding No Prostate Cancer on the Active Surveillance Confirmatory Biopsy: Implications for Pathological Progression

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Introduction and Objectives: A significant proportion of men are consistently reported to have no cancer on the second, also known as the confirmatory, biopsy (B2) for active surveillance (AS). We investigate if men on AS with no cancer found at B2, are less likely to undergo subsequent pathological progression.

Methods: Patients were identified from our tertiary care AS database (1997-2012). Eligibility criteria were PSA ≤10, clinical stage ≤T2, ≤3 positive cores, no core >50% and age ≤75. Patients who did not undergo a third or subsequent biopsy, because of either ceasing AS after the second biopsy or having insufficient follow up, were excluded. The remaining patients (n=286) were dichotomized on the basis of cancer status (yes or no) at B2. A Cox proportional hazards model was used to examine if absence of cancer at B2 was a predictor for progression. Pathological progression was defined as grade (GS ≥7) and/or volume (PCores >3, >50% single corSe involved).

Results: Of the 286 patients, 149 (52%) had no cancer and 137 (48%) had cancer without progression and remained on AS. The median follow-up for was 41 months, (IQR 26.5-61.9). The proportion of patients that re-classified on subsequent biopsies was 23.5% (no cancer group) and 40.1% (cancer group). Grade-related progression still occurred in the no cancer group (n=26/149, 17.5%). Five-year pathological progression-free survival, stratified by cancer status on B2, was 85.2% (no cancer group) and 67.3% (cancer group) (log rank, p=0.002).

No cancer at B2 was associated with a 54% reduction in risk of subsequent progression (HR 0.46, p=0.002). Increasing age (HR 1.06, p=0.001) and PSA density (HR 1.49, p=0.04) were predictors of progression.

Conclusions: We found absence of cancer on the second biopsy is associated with a significant decreased risk of pathological progression. However, grade-related progression still occurs so re-biopsy remains an essential component of follow-up in all patients on AS.

POD-01.03

Radical Prostatectomy versus Radiotherapy versus Observation Among Older Patients with Clinically Localized Prostate Cancer: A Comparative Effectiveness Evaluation

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Introduction and Objectives: There is currently a lack of consensus of the most optimal primary treatment strategy for patients with clinically localized prostate cancer (PCa). Our objective was to compare efficacy between radical prostatectomy (RP), radiotherapy, and observation with respect to overall survival (OS).

Methods: Using data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database, 67,087 men with localized PCa were identified (1988--2005). Prevalence of initial treatment strategy was quantified according to their life expectancy (LE, <10 vs. ≥10 years) at initial diagnosis and tumour stage. To reduce unmeasured bias associated with treatment, instrumental variable analysis was performed. Stratified (stage and LE) Cox regression and competing-risks regression analyses were generated for prediction of OS and cancer-specific mortality, respectively.

Results: Among patients with <10 years of LE, most men were treated with radiotherapy (49%) or observation (47%). Among patients with ≥10 years of LE, most people received radiotherapy (49%), followed by RP (26%). In men with <10 years of LE, RP and radiotherapy were not different with respect to OS (HR: 0.81, 95% CI: 0.45-1.48, p=0.499). Conversely, in men with ≥10 years of LE, RP was associated with an improved OS compared to observation (HR: 0.59, 95% CI: 0.49-0.71, p<0.001) and radiotherapy (HR: 0.66, 95% CI: 0.56-0.79, p<0.001). Similar results were recorded in competing-risks regression analyses.

Conclusions: In patients with an estimated LE ≥10 years at initial diagnosis, RP is associated with improved survival compared to radiotherapy and observation, regardless of disease stage.

POD-01.04

Impact of Enzalutamide on Time to First Skeletal Related Event (SRE) and Pain in the Phase 3 Affirm Study

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Introduction and Objectives: Enzalutamide (ENZA) inhibits androgen binding to AR, AR nuclear translocation, and AR association with DNA. AFFIRM (NCT00974311) demonstrated that ENZA increased survival by 4.8 months (p<0.0001, HR 0.63) vs. placebo (PLA) in metastatic castration-resistant prostate cancer patients (patients) post-docetaxel.

Methods: Patients were randomized 2:1 to ENZA 160 mg/d or PLA. Corticosteroids were allowed but not required. Patients were stratified by baseline (BL) ECOG and mean pain score (BPI-SF question #3 [Q3]). SRE was defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. Pain was assessed using patient diaries, FACT-P, BPI-SF. Pain palliation was based on mean of worst pain over 7 days and analgesic use in patients with disease-related pain.

Results: 800 patients were randomized to ENZA, 399 to PLA. At BL, 8.5% had ECOG=2, 28% BPI-SF Q3 score ≥4. Median time to first SRE was 16.7 months (14.6, 19.1) for ENZA, 13.3 months (9.9, NYR) for PLA (HR 0.69, p=0.0001). Pain palliation assessed by patient diaries (≥30% reduction in mean pain score at week 13 vs. BL without a ≥30% increase in analgesic use) was achieved by 45% ENZA patients compared to 7% PLA patients (p=0.0079). In evaluable patients (both BL and week 13 BPI-SF Q3 scores), 28% ENZA and 39% PLA patients (p=0.0018) had pain progression assessed by patient diaries (increase over BL in mean pain score). Median time to pain progression (confirmed increase in FACT-P score of "I have pain") was not yet reached vs. 13.8 months for ENZA and PLA (p=0.0004, HR 0.56). There was a mean reduction in pain severity (average of 4 severity items of the BPI-SF) of 0.65 favouring ENZA (p<0.001). Pain interference (average of 7 interference items of the BPI-SF) was reduced by a mean of 0.76 in the ENZA group vs. PLA (p<0.001).

Conclusions: Enzalutamide significantly delayed the time to first SRE and had a consistently favourable and significant impact on measures of pain vs. PLA.

POD-01.05

Final Analysis of Intergroup (NCIC-CTG, CUOG, SWOG, MRC-UK) Randomized Phase III Study of Androgen Deprivation Therapy(ADT) and Radiation Therapy (RT) in Locally Advanced Prostate Cancer

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Background: Interim analysis of NCIC Clinical Trials Group (NCIC CTG) PR.3/Medical Research Council (MRC) UK PR07 trial demonstrated an overall survival (OS) benefit of RT when added to ADT in patients with locally advanced prostate cancer. We now present the protocol-specified final analysis of the study with mature outcome data.

Methods: Patients with locally advanced (T3/T4, N0/NX) prostate cancer (1057) or organ-confined disease (T2, N0/NX) with either a PSA >40 µg/l (119) or PSA >20 µg/l and Gleason >8 (25) were randomized to lifelong ADT with or without RT (65-69 Gy to prostate + seminal vesicles with or without 45 Gy to pelvic nodes). The primary outcome measure was OS; secondary outcome measures included disease-specific survival (DSS), time to disease progression and effect on quality of life. Final analysis was planned for after 421 events (deaths).

Results: 1205 patients were randomized between 1995 and 2005, 602 to ADT alone and 603 to ADT+RT. With median follow-up of 8.0 years, 465 patients have died (260 ADT and 205 ADT+RT). The addition of RT to ADT significantly improved OS (HR 0.70, 95% CI 0.57-0.85, p=0.001). 199 patients (43%) died of disease and/or treatment (134 on ADT alone and 65 on ADT+RT). ADT+RT significantly improved DSS over ADT alone (HR 0.46, 95% CI 0.34-0.61, p<0.0001). The addition of RT to ADT had a small detrimental effect on late gastrointestinal toxicity (>grade II proctitis, 0.3% ADT alone, 1.0% ADT+RT.

Conclusions: The final, mature data from this study indicate a sustained and substantial overall survival and disease specific survival benefit for the combined modality approach (ADT+RT) in the management of patients with locally advanced prostate cancer with minimal increase in late treatment toxicity. The benefits of combined modality treatment (ADT+RT) should be discussed with all patients.

POD-01.06

The Association between Finasteride Use and High-grade or Lethal Prostate Cancer

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Introduction and Objective: Despite the widespread use of 5-alpha reductase inhibitors (5-ARIs) for benign prostatic hyperplasia (BPH), there is much controversy regarding the potential risk of high-grade prostate cancer when 5-ARIs are used for chemoprevention. Our objective was to determine the association between finasteride use and the development of total, high-grade or lethal prostate cancer.

Methods: The Health Professionals Follow-up Study is a prospective cohort of United States male health professionals who were 40 to 75 years old at baseline in 1986. Finasteride use was assessed on questionnaires every two years from 1996, and 38,430 men who were cancer-free in 1996 were followed for prostate cancer diagnosis until 2010. Cox proportional-hazard models were used to estimate risk associated with finasteride use, adjusting for possible confounders.

Results: During 452,576 person-years of follow-up, we ascertained 3710 prostate cancer cases, 578 of which were advanced and 463 of which were high-grade. Of 38,419 men at baseline in 1996, 2920 (7.6%) reported use of Finasteride between 1986-2010. The age-adjusted relative risk for ever-use of Finasteride compared with never-use was 1.04 (95% CI=0.89-1.22) for total disease. After adjusting for confounders, ever use of Finasteride was associated with significantly lower risk of total disease, Gleason 7 and low-grade disease. The multivariable-adjusted relative risk was 0.77 (95% CI=0.65-0.90) for total disease, 0.66 (95% CI=0.49-0.89) for Gleason 7 disease, and 0.73 (95% CI=0.57-0.94) for low-grade disease. Finasteride use was not associated with risk of high-grade (RR=1.00, 95% CI=0.67-1.49) or lethal disease (RR=0.95, 95% CI=0.56-1.63).

Conclusions: Finasteride use was not associated with either lowering or increasing the risk of high grade, or lethal prostate cancer. Finasteride use was, however, associated with a decreased risk of overall, low-grade, and Gleason 7 prostate cancer.