Podium Session 4: Prostate Cancer
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POD-04.01

Use of abiraterone in the management of castration-resistant prostate cancer in Quebec: A real-life cost-effectiveness study

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Introduction and Objectives: Abiraterone acetate (Abi) therapy showed survival benefits in the treatment of castration-resistant prostate cancer (CRPC) in phase III trials. In Quebec, Abi reimbursement was approved for docetaxel (Doc) naïve and refractory patients in 2014 and 2012, respectively. This study evaluated the cost-effectiveness and survival impact of Abi in the management of CRPC post-docetaxel.

Methods: The study cohort was selected from the: Régie de l'Assurance Maladie du Québec (RAMQ) and Med-Echo databases. It consisted of patients with CRPC starting chemotherapy or abiraterone treatments in between 2009-2010 (Doc), defined as pre-Abi era, and 2012-2013 (Doc+Abi), and defined as Abi era. Survival was evaluated by Kaplan-Meier and the difference in survival between pre-Abi and Abi eras by log-rank test. Association between Abi exposure and survival was evaluated by cox proportional hazards model adjusted for co-variables. The incremental cost-effectiveness ratio (ICER) was obtained by dividing changes in costs (Doc alone, Doc+Abi) and survival in the two periods.

Results: Survival was significantly increased by the addition of Abi to CRPC management. Mean survival was 11.47 (±0.6; N=115) vs. 15.26 (± 0.85; N= 67) months in the pre-Abi vs. Abi era ($p<0.001$). Mean treatment duration for Abi was 163 days (±108.7) and for chemotherapy during Abi period was 4.4 cycles (±3.1) and 4.6 cycles in the pre-Abi era (±4.2). The adjusted hazard ratio when comparing pre-Abi vs. Abi era was 1.32 (95%CI 0.98-1.78). The primary therapy cost per patient for Doc group was $3,680 and for Doc+Abi group was C$49,650. As expected, the addition of Abi resulted in a cost increment estimated at C$45,970/patient. The ICER was C$145,569 per life-year gained.

Conclusions: Our real-life study indicates that patients receiving Abi plus Doc had a survival benefit when compared to the group receiving chemotherapy alone. Addition of Abi was associated with an important ICER.

POD-04.02

The association between statin use and outcomes in patients initiating androgen deprivation therapy

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Introduction and Objectives: Results of studies regarding the association between statin use and biochemical recurrence after surgery or radiotherapy for localized prostate cancer are conflicting. A few studies have observed favorable associations between statins and prostate cancer-specific (PCSM) and overall mortality (OS), however, this has not been studied in an advanced disease cohort, nor is there any data on the combination of statins and androgen deprivation therapy (ADT).

Methods: Patients with PSA >3 ng/mL after >1 year following primary or salvage radiotherapy (RT) were enrolled in a randomized trial of intermittent (IAD) vs. continuous (CAD) ADT (NCT00003653). Statin use at baseline and during the study was captured and modeled as a time-dependent covariate. The primary end-point was OS. Models were adjusted for age, time from RT to ADT and PSA at baseline. As results were nearly identical between the IAD and CAD arms they are reported as aggregates unless otherwise indicated.

Results: Of 1364 patients enrolled, 585 (43%) reported statin use during the study. Statin users were younger (72.7 vs. 73.8, $p=0.001$) and less likely to have PSA >15 (20 vs. 25%, $p=0.04$). Median follow-up was 6.9 years (range 2.8 – 11.2) and 524 patients (38%) have died. Statin use was associated with a reduced risk of overall death (HR: 0.64; 95% C.I. 0.53 – 0.78, $p<0.001$) and PCSM (HR: 0.64, 95% C.I. 0.48 – 0.86, $p=0.003$). Statin users had 14% longer time to castration resistance but this did not reach statistical significance ($p=0.15$). In the IAD arm, statin users had more off-treatment intervals ($p=0.04$) and longer time off-treatment (median: 0.85 vs. 0.64 years, $p=0.06$). Across 6 functional domains, statin users reported better quality of life scores.

Conclusions: In men treated with ADT following primary or salvage RT, statin use was associated with improved overall and prostate cancer-specific survival and improved quality of life. In patients treated with IAD, statin use was associated with more off-treatment intervals and longer time off-treatment. A prospective trial of statins in men commencing ADT is warranted to confirm this observation.

POD-04.03

Systematic review and meta-analysis of decision aids for localized prostate cancer treatment choice

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Introduction and Objectives: Patients diagnosed with localized prostate cancer need to make critical treatment decisions sensitive to their values and preferences. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) of decision aids for localized prostate cancer to evaluate their role in facilitating these decisions.

Methods: We searched MEDLINE, EMBASE, PsycINFO, CINAHL, Cochrane databases, without language limits up to August 2014. We performed

screening, data extraction, risk of bias and quality assessments in duplicate, independently. We sent our data extraction to the original authors for verification. We analyzed treatment effects between decision aids and usual care using the DerSimonian-Laird random-effects inverse variance method for continuous outcomes and Cochran-Mantel-Haenszel method for treatment choice.

Results: Of 2,737 reports, 14 RCTs proved eligible (n=3,377 men). Of these, 11 RCTs compared decision aids to usual care and 3 to other decision aids. Overall, 12 RCTs were at high risk of bias; only 2 were at low risk of bias. We evaluated 9 decision aids provided by authors. Decision aids reported positive and negative consequences of alternative management strategies well (9 of 9, 100%) but presented event rates less frequently (56%), and did not typically make direct comparison of probabilities possible (33%). Two trials suggested a modest positive reduction in decisional regret (Fig. 1). Results varied widely for decisional conflict (4 trials), satisfaction with decision (2 trials) and knowledge (2 trials). We found no impact on treatment choices (6 trials) (Fig. 2). The decision aids tested in these trials were designed to provide patients with information to prepare for the clinical encounter. No decision aid was primarily designed for use in the clinical encounter and no trial directly assessed

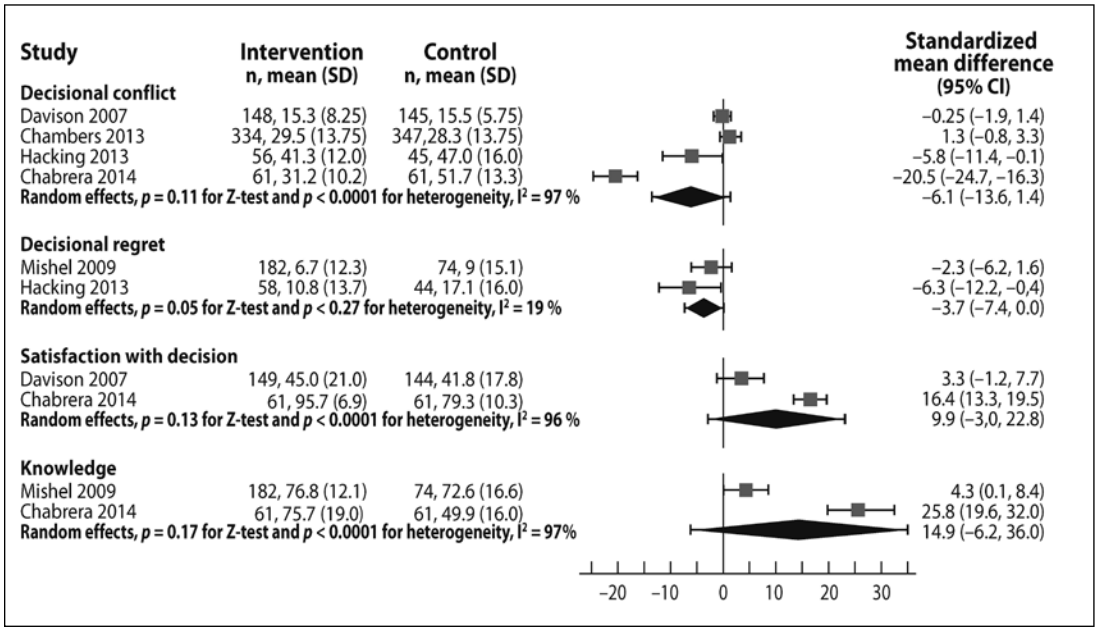

Fig. 1. POD-04.03. Forest plot of shared decision making outcomes for trials comparing decision aid to usual care.

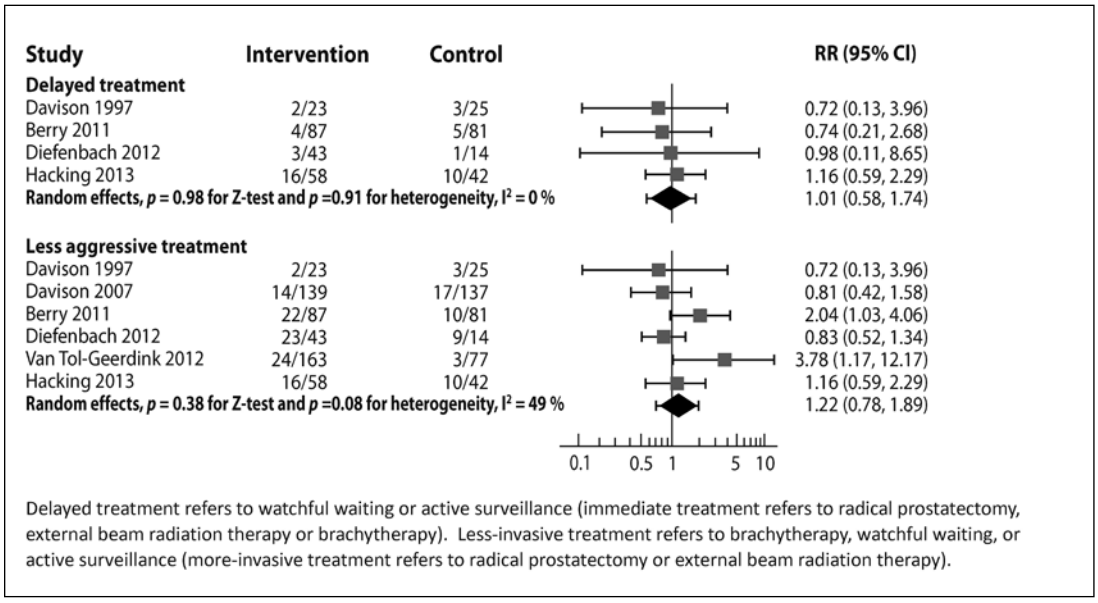

Fig. 2. POD-04.03. Forest plot of treatment choice for trials comparing decision aid to usual care.

the impact of the decision aid on collaborative deliberation and shared decision making.
Conclusions: Limited evidence suggests variable impact of existing decision aids on a limited set of decisional processes and outcomes. Work in this area would benefit from user-centered design of decision aids that promote shared decision making.

POD-04.04

The adoption of active surveillance for the management of prostate cancer in Ontario: A population based-study

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Introduction: Expectant management such as active surveillance (AS) and watchful waiting (WW) are recognized as treatment options for prostate cancer (PCa), especially for low-risk disease. Although several single-center studies have reported the merit of expectant therapies, there seems to be a delayed uptake of these treatment options at a population-based level. The objectives of this study were to examine the trends in AS and WW in a contemporary cohort and to examine the probability of discontinuing AS over time.
Methods: This is a retrospective population-based cohort study, in which we used administrative hospital data, physician billing codes and cancer registry data to identify men diagnosed with any-risk localized adenocarcinoma of the prostate in Ontario between 2002 and 2010. Rates of AS, WW and definitive treatment were then estimated. AS was defined as a patient who had a repeat biopsy following diagnosis before any definitive treatment was instituted. Rates of expectant therapies were compared over time using the Cochrane-Armitage test for trend. The probability of discontinuing AS over time was estimated using cumulative incidence function.
Results: Among the 44 292 patients included in this study, 21.0%, 9.4% and 69.6% were respectively managed by AS, WW and definitive treatment during the study period. Rates of expectant therapy increased from 26.4% in 2002 to 36.0% in 2010. More specifically, the rates of AS increased from 14.7% in 2002 to 23.5% in 2010 ($p<0.001$). Overall, 61.9% of the patients managed by AS eventually received definitive treatment. The majority of these patients were treated within 6 months of the confirmatory biopsy (77.8%) and 60.7% received definitive treatment within the first year following diagnosis. The cumulative probability of discontinuing AS at 1-, 2-, 3-, 4- and 5-year was respectively 39.6%, 49.3%, 55.4%, 60.4% and 64.2%.
Conclusions: Given an any-risk PCa population-based cohort, the use of expectant therapy and more specifically AS was frequently applied. Moreover, the rates seemed to increase over time. However, 61.9% of these patients eventually moved on to receive definitive treatment. Due to the limitations of the administrative data, rates of AS according to specific risk-groups and reasons for the discontinuation of AS were unavailable at this time.

POD-04.05

Outcomes of active surveillance for favourable risk prostate cancer: The 21 year Vancouver experience

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Introduction and Objectives: Active surveillance (AS) is widely recommended as a standard initial management option in men diagnosed with favorable risk, apparently localized prostate cancer (PCa). Superior oncological control of immediate radical prostatectomy (RP) over delayed RP following AS has not been definitively proven. Our centre has offered AS to men with both low and intermediate risk PCa based on patient and physician accepted balance of competing risks. We aimed to describe their outcomes, compare outcomes between risk groups and identify predictors of progression.
Methods: Men managed with AS at the University of British Columbia, Vancouver, were classified as Low, Intermediate and High risk based on the NCCN classification. Clinical and demographic characteristics , progression to Active treatment, cancer progression on biopsy and PSA doubling time were compared between groups. CAPRA scores were calculated to help differentiate the spectrum of intermediate disease. Rates of unfavourable pathology and PSA failure following radical prostatectomy were analysed. Overall and cancer-specific survival for the entire cohort was determined.
Results: Between 1993 and 2014, 915 men had AS for their initial management. 651 met the strict inclusion (including 142 Intermediate or High Risk) criteria to exclude those who had watchful waiting. The median follow-up was 4.5 years (range 0.6 – 19.1). Gleason score upgrade on repeat biopsy while on AS occurred in 209 (32.1%) cases. 259 patients (39.7%) underwent active treatment. There was no significant difference in the treatment rates between the low and intermediate NCCN risk groups. However, cancer progression-free survival was higher in the CAPRA low risk group compared to the intermediate risk group ($p<0.05$). 203 patients had radical prostatectomy with an overall rate of unfavourable pathology (predominant Gleason pattern 4 or ≥ pT3 disease) of 36.4%. The biochemical failure rate following radical therapy was 8.1%. The 15 year metastasis free survival was 96.7%. The overall survival was 97.7%. Actuarial overall survival at 5 and 10 years was 98.6% and 94.1%. There were 2 prostate cancer deaths at 18.7 and 19.1 years of follow up.
Conclusion: Active surveillance is a justified treatment option in selected men with low and intermediate risk prostate cancer. The risk of progression to incurable prostate cancer is low. CAPRA score better discriminates low from intermediate disease compared to NCCN risk in predicting AS outcomes.

POD-04.06

An assessment of PRIAS criteria for active surveillance of clinically low-risk prostate cancer patients

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Introduction and Objectives: The PRIAS program recommends clinical criteria to identify the best candidates for prostate cancer active surveillance. The objective of this study was to compare pathologic findings and post-treatment outcomes between PRIAS eligible and PRIAS ineligible low-risk prostate cancer patients.
Methods: We reviewed consecutive radical prostatectomy patients treated prior to the common use of active surveillance (1995 to 2007). Patients were excluded if they had: intermediate or high-risk disease, prior prostate radiation, prior androgen deprivation, or >6 months between diagnosis and surgery. Pathological outcomes included stage pT3 disease, Gleason score ≥7, lymph node metastases, or any of these three features. Post-treatment outcomes included PSA recurrence and death. Univariable and multivariable analysis was used to compare outcomes between PRIAS eligible and PRIAS ineligible patients.
Results: Of 9915 radical prostatectomies, 1512 low-risk patients were included in this study. Of these, 651 (43.8%) had Gleason score ≥7, 219 (14.5%) had pT3, 10 (0.7%) had lymph node metastases, and 707 (46.8%) had at least one of these findings. PRIAS eligible patients were less likely to have Gleason score ≥7 (OR 0.61, p=<0.001), pT3 (OR 0.41, p<0.0001), nodal metastases (OR 0.37; p=0.1238), or any adverse finding (OR 0.56; <0.0001). PSA, PSA density, number of positive biopsy cores, and clinical

stage were associated with increased risk of Gleason score ≥7, pT3, or any adverse finding. There was no statistically significant difference in recurrence-free or overall survival between PRIAS and non-PRIAS cohorts following prostatectomy (HR=0.71; 95% CI: 0.46 – 1.09 and HR=0.72; 95% CI: 0.36 – 1.47, respectively).
Conclusions: Patients meeting PRIAS criteria for active surveillance have distinct pathologic differences from other low-risk patients. Pre-operative PSA, number of positive biopsy cores, and PSA density are important variables in the selection of patients for active surveillance.

POD-04.07

A randomized, double-blind, phase 2 efficacy and safety study of enzalutamide vs. bicalutamide in metastatic castration-resistant prostate

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Objectives: The phase 2 TERRAIN trial compared the efficacy and safety of enzalutamide (ENZA) vs. bicalutamide (BIC) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) who have progressed on luteinizing hormone-releasing hormone agonist/antagonist therapy or after bilateral orchiectomy while maintaining castration therapy during the study.
Methods: In this double-blind study in North America and Europe, pts were randomized 1:1 to ENZA 160 mg/day or BIC 50 mg/day. The primary endpoint was progression-free survival (PFS), defined as time from randomization to centrally confirmed radiographic progression, skeletal-related event, initiation of new anti-neoplastic therapy or death from any cause, whichever occurred first.
Results: A total of 184 pts were randomized to ENZA and 191 pts to BIC. At baseline, 73.6% of pts had an Eastern Cooperative Oncology Group performance score of 0 and median prostate-specific antigen (PSA) was 21 ng/mL. PFS increased significantly for ENZA vs. BIC (hazard ratio [HR]=0.44; 95% CI 0.34, 0.57; p<0.0001). Median PFS was longer for ENZA pts compared with BIC pts (15.7 vs. 5.8 months, respectively). Median time to PSA progression was prolonged on ENZA (19.4 months) vs. BIC (5.8 months; HR=0.28; p<0.0001). A ≥50% PSA response was achieved in 82.1% of ENZA-treated pts vs. 20.9% in BIC. Serious adverse events (AEs) were reported in 31.1% of ENZA vs. 23.3% of BIC pts. Grade ≥3 cardiac AEs were observed in 5.5% of ENZA vs. 2.1% of BIC pts. Two seizures were reported with ENZA and one with BIC. AE rates are not adjusted for time on treatment.
Conclusions: ENZA had significantly greater efficacy than BIC, with superior PFS and PSA response rates. ENZA showed safety broadly consistent with its known safety profile in pts with mCRPC.