What's new in prostate cancer research?

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New sub-classification system for intermediate-risk prostate cancer patients may improve clinical decision-making

The preoperative D'Amico system classifies T1c prostate cancer into three risk groups based on their prostate-specific antigen (PSA) values: less than 10 ng/mL, 10.1–20 ng/mL, and higher than 20.1 ng/mL, corresponding to low-, intermediate- and high-risk disease categories, respectively.[1] However, prognosis can vary widely among men who fall into the intermediate-risk category and additional stratification of this heterogeneous group could aid in optimizing management of this population. A new sub-classification was recently proposed, whereby "unfavourable intermediate-risk" (UIR) prostate cancer was defined as any intermediate-risk prostate cancer with a primary Gleason pattern of 4, a percentage of positive biopsy cores higher than 50%, or more than one intermediate risk factor (cT2b–c, PSA 10–20 ng/mL or Gleason score 7).[2] A validation study for this new sub-classification system was presented at the EAU 2016. The multicentre study enrolled 4028 patients with intermediate-risk prostate cancer who had been treated by radical prostatectomy between 2000 and 2011.[3] After a median followup of 44.4 months, patients with UIR had poorer PSA recurrence-free survival than those without UIR (68.8% vs. 83.5%; hazard ratio [HR] 2.05 [95% CI 1.78–2.36]; p=0.0193) (Fig. 1). Men in the UIR group also had a significantly higher need for adjuvant therapy. This common-sense approach to stratifying men with intermediate-risk prostate cancer was seen as reasonable by Canadian urologists attending the session; however, it was suggested that more robust predictions would likely be gained through the use of more fluid nomograms.

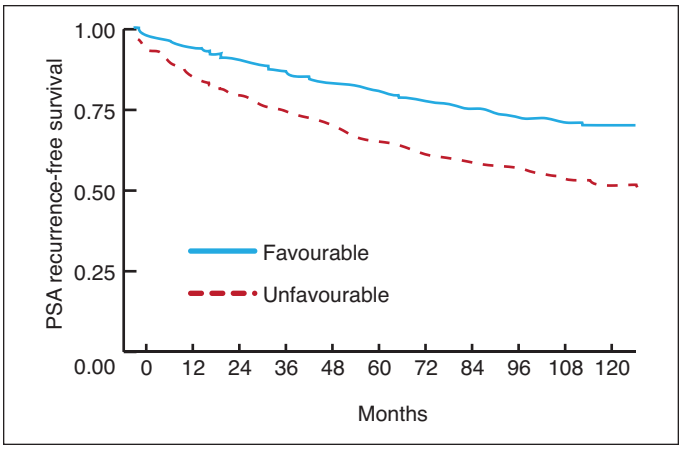

Fig.1. Prostate-specific antigen (PSA) recurrence-free survival following radical prostatectomy in 4028 patients with either "favourable" or "unfavourable" intermediate-risk prostate cancer.[3]

Salvage radical prostatectomy offers good long-term oncological outcomes after radiotherapy in patients with biopsy-proven recurrent prostate cancer

PSA recurrence is common following curative treatment. While most patients who fail primary radiation therapy will receive palliative hormonal therapy, there is a subset with persistent/recurrent cancer in the prostate only who may benefit from salvage extirpative or ablative local therapy. Vilaseca and colleagues from Spain presented results from their retrospective review of 251 men who underwent salvage radical prostatectomy for biopsy-proven radio-recurrent prostate cancer after external beam radiation therapy (EBRT), brachytherapy, or both.[4] Fifty (50) patients died, of whom 27 died due to prostate cancer. Five- and 10-year cancer-specific survival rates were 92% (95% CI 87–96%) and 78% (95% CI 67–86%), respectively. The five- and 10-year overall survival (OS) rates were 87% (95% CI 81–92%) and 64% (95% CI 52–74%), respectively (Fig. 2). The one- and three-year rates of bladder neck cancer (BNC)-free survival were 81% (95% CI 75–85%) and 73% (95% CI 67–79%), respectively.

The researchers identified 221 men who had undergone an open approach and 30 men who underwent minimally invasive surgery. BNC-free survival was significantly higher among patients treated with minimally invasive surgery than among those who received open salvage radical prostatectomy (log-rank p=0.007). This study suggests that, although salvage treatment is generally associated with poor functional outcomes and complications, minimally invasive techniques are associated with better anastomotic stricture-

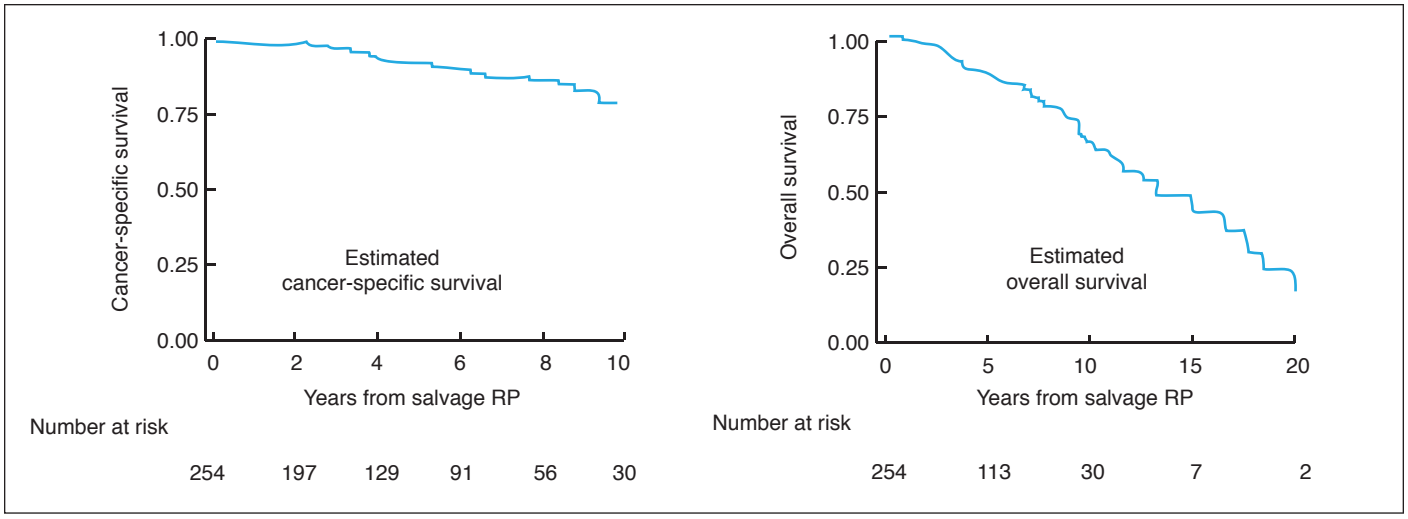

Fig. 2. Estimated cancer-specific survival and overall survival in 251 men who underwent salvage radical prostatectomy (RP) for biopsy-proven radio-recurrent prostate cancer after external beam radiation therapy, brachytherapy, or both.[4]

free survival than open techniques. A potential bias of this single-centre study is that patients were likely selected based on their presumed fitness for surgery. Nonetheless, these results are very promising.

An algorithm-based protocol may streamline community followup of men with stable prostate cancer

The routine followup of men with prostate cancer has been identified as a major contributing factor to reduced outpatient capacity and adverse followup ratios. Men with asymptomatic prostate cancer who require PSA surveillance alone after undergoing definitive management of prostate cancer often complain of long clinic waits, short appointments, and limited medical input. To address these issues, a group from the U. K. recently implemented a novel algorithm-based discharge program for the community followup of men with stable prostate cancer.[5] A total of 573 men were discharged to one of four discharge pathways: watchful waiting (n=169), androgen-deprivation therapy (ADT) (n=229), post-prostatectomy (n=95) and post-radiotherapy (n=80). Primary care providers were instructed to implement specific surveillance measures and refer patients back to the specialist if their PSA rose to a pre-defined threshold. After a minimum followup of 12 months, 54 men had a PSA threshold breach: 48 were promptly referred back to the specialist, three refused, one died prior to referral from an unrelated cause, two were late referrals (four months), and three were lost to followup due to database non-registration and were subsequently recalled, none of whom had a PSA-threshold breach. Overall, this algorithm-based protocol was found to be effective and oncologically safe for the controlled discharge of men from specialist to primary care. Similar issues with capacity and wait times exist in Canada. With an increased mandate for many cancer centres to disperse patients back in to the community, a protocol such as this could be applied in Canadian centres, albeit with more specific guidance for primary care physicians on when to refer patients back to the specialist.

Earlier use of chemotherapy benefits patients with metastatic prostate cancer

Two recent studies — GETUG-15[6] and CHAARTED[7] — have evaluated whether to initiate chemotherapy in hormone-naïve patients with newly diagnosed metastatic prostate cancer with conflicting results. A group of European urologists debated this topic at the EAU 2016.[8] While GETUG-15 found no survival benefit for the addition of docetaxel to ADT compared with ADT alone for patients with metastatic non-castrate prostate cancer, patients in CHAARTED who received six cycles of docetaxel at the beginning of ADT lived significantly longer than those who received ADT alone. In CHAARTED, positive survival results were more apparent in the subgroup of patients with high-volume metastases; followup time for patients with low-volume metastases was insufficient to reach the median survival.

More recently, the STAMPEDE trial compared the addition of zoledronic acid (n=593), docetaxel (n=592), or their combination (n=593) with standard of care vs. standard of care alone (n=1184) in men with newly-diagnosed "high-risk" prostate cancer.[9] High-risk prostate cancer was defined as metastatic, node-positive, or the presence of two or more of stage T3/4 disease, PSA 40 ng/mL or higher, or Gleason grade 8–10. While no benefit was shown for the addition of zoledronic acid to standard of care, docetaxel chemotherapy, given at the time of long-term hormone therapy initiation, improved both failure-free survival (HR 0.62; 95%

CI 0.54–0.70; p=0.134×10–12), and OS (HR 0.78, 95% CI 0.66–0.93; p=0.006). Similar to the CHAARTED results, there was also a notable survival benefit for the subset of patients with metastatic disease. A recent meta-analysis of GETUG, CHAARTED, and STAMPEDE revealed a 15% reduction in failure-free survival and a 10% improvement in survival at four years with the addition of docetaxel to standard of care. Taken together, these data suggest that the addition of docetaxel to standard of care should be considered standard care for men with M1 hormone-sensitive prostate cancer who are starting treatment for the first time.[10]

References

1. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280:969-74. http://dx.doi.org/10.1001/jama.280.11.969
2. Zumsteg ZS, Spratt DE, Zhang Z, et al. A new risk classification system for therapeutic decision-making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. *Eur Urol* 2013;64:895-902. http://dx.doi.org/10.1016/j.eururo.2013.03.033
3. Beauval JB, Ploussard G, Ouzzane A, et al. A new sub-classification system for decision making with intermediate-risk prostate cancer patients treated by radical prostatectomy: A multicentre study. *Eur Urol Suppl* 2016;15(suppl 3):e172. http://dx.doi.org/10.1016/S1569-9056(16)60174-4
4. Vilaseca CA, Nguyen D, Tin A, et al. Long-term oncological outcomes of salvage radical prostatectomy for radio-recurrent/persistent prostate cancer after radiation therapy. *Eur Urol Suppl* 2016;15(suppl 3):e433. http://dx.doi.org/10.1016/S1569-9056(16)60435-9
5. Goodall P, Little J, Robinson E, et al. Initial experience of an algorithm-based protocol for the community followup of men with stable prostate cancer. *Eur Urol Suppl* 2016;15(suppl 3):e68. http://dx.doi.org/10.1016/S1569-9056(16)60070-2
6. Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): A randomized, open-label, phase 3 trial. *Lancet Oncol* 2013;14:149-58. http://dx.doi.org/10.1016/S1470-2045(12)70560-0
7. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* 2015;373:737-46. http://dx.doi.org/10.1056/NEJMoa1503747
8. Miller K, Clark NW, Mottet N. Debate: When is chemotherapy indicated in hormone-naïve prostate cancer in 2016? European Association of Urology Congress; Munich; March 11-15, 2016. *Eur Urol Suppl* 2016;15(suppl 3):e1013.
9. James ND, Sydes MR, Clarke NW, et al. STAMPEDE investigators. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): Survival results from an adaptive, multiarm, multistage, platform randomized, controlled trial. *Lancet* 2016;387:1163-77. http://dx.doi.org/10.1016/S0140-6736(15)01037-5
10. Vale CL, Burdett S, Rydzewska LH, et al. STOpCaP Steering Group. Addition of docetaxel or bisphosphonates to standard of care in men with localized or metastatic, hormone-sensitive prostate cancer: A systematic review and meta-analyses of aggregate data. *Lancet Oncol* 2016;17:243-56. http://dx.doi.org/10.1016/S1470-2045(15)00489-1