What is appropriate neoadjuvant/adjuvant androgen deprivation for high-risk/locally advanced prostate cancer?

What is appropriate neoadjuvant/adjuvant androgen deprivation for high risk/locally advanced prostate cancer?

Mikio Namiki and Hiroyuki Konaka

Department of Integrative Cancer Therapy and Urology

Kanazawa University Graduate School of Medical Science

13-1 Takaramachi, Kanazawa City, Ishikawa 920-8640, Japan

Correspondence: Dr Mikio Namiki (namiki1@kenroku.kanazawa-u.ac.jp)

The majority of low-risk patients with clinically localized prostate cancer have a high likelihood of disease-free survival, regardless of the treatment option chosen[1)]. In contrast, patients with high-risk prostate cancer with high Gleason score, elevated PSA level, and advanced clinical stage have a high probability of treatment failure after initial management by single-treatment modalities, such as radical prostatectomy (RP), external beam radiation therapy (EBRT), or brachytherapy[2, 3)]. Therefore, it is extremely important to establish the most effective treatment strategy for patients with high-risk prostate cancer. As high-risk patients may have locally advanced disease with direct extension and/or micrometastases, various combinations of treatments have been developed to augment cancer-specific survival. Neoadjuvant and/or adjuvant androgen deprivation therapy (ADT) offer synergistic enhancement of RT or RP due to induction of apoptosis. Moreover, ADT may play a role in elimination of occult systemic disease[4)]. Whereas many studies have demonstrated benefits of ADT used in conjunction with EBRT to treat locally advanced prostate cancer[5, 6)], questions and criticisms remain, including the details of the duration, timing, and contents of ADT.

A recent report[7)] by Denham et al.offered some insight into the above questions.

The aim of the study (TROG 96.01 trial) was to assess whether 3-month or 6-month short-term neoadjuvant ADT could decrease clinical progression and mortality rate after radiotherapy (EBRT) for locally advanced prostate cancer. In this study, 818 men with T2b, T2c, T3, and T4 N0 M0 prostate cancer were randomly assigned to receive radiotherapy alone, 3 months of neoadjuvant ADT plus radiotherapy, or 6 months of neoadjuvant ADT plus radiotherapy. The radiotherapy dose for all groups was 66 Gy, delivered to the prostate and seminal vesicles (excluding pelvic nodes). Neoadjuvant ADT consisted of 3.6 mg of goserelin every month and 250 mg of flutamide given orally three times a day. Primary endpoints were prostate cancer-specific mortality and all-cause mortality. After a median

follow-up of 10.6 years, 3 months of neoadjuvant ADT decreased the cumulative incidence of PSA progression ($p=0.003$) and local progression ($p=0.0005$), and improved event-free survival ($p<0.0001$) compared with radiotherapy alone. Six months of neoadjuvant ADT further reduced PSA progression ($p<0.0001$) and local progression ($p=0.0001$), and led to a greater improvement in event-free survival ($p<0.0001$) compared with radiotherapy alone. However, 3-month neoadjuvant ADT had no effect on distant progression ($p=0.550$), prostate cancer-specific mortality ($p=0.398$), or all-cause mortality ($p=0.180$) compared with radiotherapy alone. In contrast, 6-month neoadjuvant ADT decreased distant progression ($p=0.001$), prostate cancer-specific mortality ($p=0.0008$), and all-cause mortality ($p=0.0008$) compared with radiotherapy alone. Treatment-related morbidity was not increased with neoadjuvant ADT within the first 5 years after randomization.

From the above results, it was concluded that 6 months of neoadjuvant ADT combined with radiotherapy is an effective treatment option for locally advanced prostate cancer, particularly in men without nodal metastases or preexisting metabolic comorbidities.

As the prolonged use of ADT may result in an increase in adverse events, investigation of the optimal duration of neoadjuvant and/or adjuvant ADT with maximized outcome and minimized toxicity is a logical step in the management of localized high-risk prostate cancer. Although this trial showed that 3-month neoadjuvant use had no beneficial effects on distant progression, prostate cancer-specific mortality, or all-cause mortality compared with radiotherapy alone and that 6-month neoadjuvant ADT decreased distant progression, prostate cancer-specific mortality, and all-cause mortality compared with radiotherapy alone, further longer neoadjuvant ADT may produce better outcomes than 6 months of neoadjuvant ADT. Trials regarding adjuvant ADT have already demonstrated the superiority of longer periods of adjuvant ADT. Therefore, with sufficient care to

prevent adverse effects due to ADT, better outcomes with further longer neoadjuvant ADT may be achieved.

Trimodality treatment (EBRT + brachytherapy ± ADT) has attracted attention as another method to produce better outcomes for high-risk prostate cancer. According to the American Brachytherapy Society (ABS), brachytherapy alone is not recommended for high-risk PCa but can be used as a boost in conjunction with EBRT[8]. In this multimodal approach, the combined brachytherapy and EBRT theoretically delivers a possible escalated dose to the prostate and at the same time to extracapsular cancer extension. Although the ABS provides no clear indications for neoadjuvant and/or adjuvant ADT with combination of brachytherapy and EBRT in high-risk prostate cancer, the duration of ADT could be reduced with such multi-modality RT. According to NCCN Guidelines™ version 1, 2011, the trimodality treatment (EBRT + brachytherapy ± short-term ADT) is added as a recommended arm in cases of high- and very high-risk prostate cancer.

In contrast to the many efforts to develop better treatments for RT with ADT, there have been few clinical trials investigating the effectiveness of neoadjuvant or adjuvant ADT with RP. One reason for this is that early studies of neoadjuvant ADT did not confirm the improvement of overall survival despite improvements in the pathological findings. Another reason is that surgeons may have less interest in medical treatments, such as ADT. However, surgeons should consider the best methods of improving the results in cases of high-risk prostate cancer, because recent reports have demonstrated the superiority of RT for high-risk prostate cancer compared with RP[9].

Finally, it should be stressed that it may be possible to eradicate high-risk or locally advanced prostate cancer with appropriate use of ADT in combination with RT or RP. Therefore, further well-designed clinical trials are required.

References

1. Cooperberg MR, Lubeck DP, Meng MV, Mehta SS, Carroll PR: The changing face of low-risk prostate cancer: trends in clinical presentation and primary management. J Clin Oncol 2004, 22(11):2141-2149.

2. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, et al: Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998, 280(11):969-974.

3. Bastian PJ, Gonzalgo ML, Aronson WJ, Terris MK, Kane CJ, et al: Clinical and pathologic outcome after radical prostatectomy for prostate cancer patients with a preoperative Gleason sum of 8 to 10. Cancer 2006, 107(6):1265-1272.

4. Zietman AL, Shipley WU: Androgen deprivation and radiation therapy in prostate cancer: the evolving case for combination therapy. International Journal of Radiation Oncology, Biology, Physics 1997, 37(2):245-246.

5. Horwitz EM, Bae K, Hanks GE, Porter A, Grignon DJ, et al: Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. J Clin Oncol 2008, 26(15):2497-2504.

6. Bolla M, de Reijke TM, Van Tienhoven G, Van den Bergh AC, Oddens J, et al: Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med 2009, 360(24):2516-2527.

7. Denham JW, Steigler A, Lamb DS, Joseph D, Turner S, et al: Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomized trial. Lancet Oncol, published online March 25, 2011.

8. Nag S, Beyer D, Friedland J, Grimm P, Nath R: American Brachytherapy Society (ABS) recommendations for transperineal permanent brachytherapy of prostate cancer. International Journal of Radiation Oncology, Biology, Physics 1999, 44(4):789-799.

9. Bittner N, Merrick GS, Wallner KE, Butler WM: Interstitial brachytherapy should be standard of care for treatment of high-risk prostate cancer. Oncology 2008, 22(9): 995-1017.