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Master lecture

Minimizing the side effects of ADT

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Androgen deprivation therapy (ADT) is widely used in the management of prostate cancer at essentially all stages and presentations. For example, in addition to its obvious key role in the management of metastatic disease, ADT is commonly used in combination with external beam radiation therapy (EBRT) for high risk or locally advanced disease for durations of 6 months to 3 years. In this scenario several large mature multi-institution randomized trials have shown a survival benefit.[1–3] For intermediate risk disease the addition of ADT to conventional dose radiotherapy (65–70 Gy) improves both biochemical disease free survival and overall survival.[4]

However, in both intermediate and high risk disease, the role of ADT is being challenged and is beginning to decrease in importance as the ability to deliver very high biologically effective doses (BED) becomes more widely available, especially though the combination of external radiotherapy and brachytherapy. Brachytherapy as a form of dose escalation, either low dose rate or high dose rate, achieves biologically effective doses much higher than can be achieved with EBRT, dramatically changing the pattern of failure.[5] Local recurrences are markedly reduced, eliminating the second wave of distant metastatic failures that emanate from uncontrolled local tumor and improving disease specific mortality.

The side effects of ADT are well documented and include not only sexual dysfunction, loss of libido and hot flashes, but also osteoporosis, obesity, insulin resistance and diabetes, alterations in lipids, cardiovascular disease, fatigue, decreased muscle mass, depression, and even cognitive dysfunction.[6] The metabolic syndrome, characterized by central obesity, elevated triglycerides, reduced high-density lipoproteins, elevated blood pressure and elevated fasting glucose is present in over 50% of men undergoing long-term ADT as compared to 22% of prostate cancer patients not receiving ADT. However, despite these common and occasionally serious side effects, ADT is frequently used in situations where evidence of benefit is lacking, such as combined with definitive radiotherapy for favorable risk prostate cancer,[7] or in the case of primary management of the elderly patient with low risk disease.[8] Large randomized trials have demonstrated not only lack of benefit but possible harm in these situations.

When ADT is indicated, patients should be informed of the potential side effects and encouraged to correct life style related co-morbidities by stopping smoking, adopting a healthy diet and commencing a regular exercise program. Their Body Mass Index should be recorded and blood pressure, blood sugar and serum lipids should be optimized. If there is a history of cardiovascular disease, assessment by a cardiologist is appropriate.

For biochemically recurrent disease after definitive therapy, a Canadian-lead international trial (NCIC PR7) has demonstrated that an intermittent approach, with 8–9 month treatment cycles interspersed with variable length off-treatment periods, results in the same overall survival as the continuous ADT approach and has advantages in terms of quality of life.[9] A similar trial for newly diagnosed metastatic disease (SWOG 9346) resulted in equivocal findings[10] but some subgroups of patients with metastatic disease, such as those who are asymptomatic, may be considered for this approach provided careful monitoring is undertaken.

Appropriately selecting patients for ADT according to established indications will minimize the number exposed, while systematic patient education prior to initiating treatment can ameliorate the side effects.

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