

comments

INTRODUCTION

This comment should start with the acknowledgement that we are firm advocates of the value of radiotherapy (RT) after radical prostatectomy (RP) in many patients with prostate cancer. However, we are concerned that a published and recently presented study (European Organization for Research and Treatment of Cancer, EORTC, Trial 22911) by Bolla *et al.* [1,2], of adjuvant RT vs observation for patients with potentially higher risk prostate cancer after RP, used endpoints to show a benefit that were not appropriate for an adjuvant treatment, and thus might give an impression of value that is not clinically meaningful.

PSA is a widely used biomarker for the diagnosis, risk prediction (prognosis) and monitoring of prostate disease activity. The attractiveness of PSA as 'a surrogate marker' in different stages of prostate cancer is obvious, as it can be substituted for the endpoint of interest in future therapeutic trials, thus obtaining the same conclusions about treatment comparisons while eliminating the need for longer follow-up for the definitive endpoint.

In clinical medicine a true endpoint for clinical benefit is defined as a characteristic or variable that reflects how a patient feels or functions, or how long a patient survives. This implies that the surrogate endpoint must be correlated with the clinical outcome, and that the surrogate endpoint must fully capture the net effect of treatment on the clinical outcome. Trials using PSA-based endpoints to 'show clinical benefit' must have adequate power to show that overall survival is no worse. In addition, systematic assessment of long-term morbidities must also be a factor, particularly in the setting of prostate cancer where the natural history is long, hence the potential for an adverse effect on quality of life. It is conceivable that despite an apparent benefit in some patients, others might have

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worse survival, as in the case of patients undergoing watchful waiting who were randomized to a high-dose bicalutamide group in the Early Prostate Cancer Program, where patient survival appeared to be reduced in patients treated with bicalutamide for localized disease [3]. Another example is the increasing high-density lipoprotein cholesterol levels (surrogate endpoint) in patients using the novel cholesteryl-ester transfer-protein inhibitor torcetrapib, which was associated with an increase in mortality [4].

Another important consideration is the timing of an intervention. An example in another disease, immediately recognised by urologists and radiation oncologists, is the timing of adjuvant chemotherapy for pathological stage II testis cancer, which was shown by a comparison of adjuvant chemotherapy vs chemotherapy at relapse [5]. That study found that there was unequivocal evidence of a favourable effect of treatment (chemotherapy), but the research question was about the timing, side-effects and degree of treatment to those who were cured by surgery alone. As it turned out, adjuvant chemotherapy and chemotherapy at relapse give similar survival rates, and so the decision on when to treat depends on the side-effects from the chemotherapy, particularly in those who might not need it, and the toxicity and reliability of the patient to actually obtain the salvage treatment if needed. An endpoint in these studies could not have been the delay in relapse after surgery. Any therapy that has some effect on the disease and could be used in an adjuvant setting might delay relapse,

but such a finding does not necessarily translate into an overall clinical or survival benefit compared to treatment later at the time of relapse, and must be carefully weighed against the disadvantage of treating several patients who were 'cured' by surgery alone.

There is indisputable evidence that some fraction of patients will have a durable PSA response after salvage RT for an increasing PSA level, and thus salvage RT affects the disease to some degree [6,7]. A delay in PSA relapse (biochemical disease-free survival) with adjuvant RT would be entirely anticipated unless the treatment was worthless, which few think is the case. Unfortunately, EORTC trial 22911 had as its primary endpoint the prolongation of biochemical progression-free survival (or delay in PSA relapse) and was powered to detect a 7.5% increase in biochemical progression-free survival [1,2]. The control arm was not early salvage RT at the time of PSA relapse. Indeed, most of the clinical failures were locoregional and half the patients in the control arm did not receive RT at any time; of the half who did receive salvage RT, many, if not most, received it for a clinically evident local recurrence, i.e. certainly not early salvage and after the patient had already reached an endpoint for failure in the study design. Not surprisingly, the study showed a benefit for adjuvant RT in delaying biochemical or clinical relapse, but no improvement in overall survival. In a similar South West Oncology Group (SWOG) study started in the late 1980s before the widespread use of PSA for monitoring after

surgery, a design of this type was understandable [8]. However, the EORTC study was undertaken in 1992 when the PSA test was better integrated into patient care.

In 2007, the EORTC 22991 study provided interesting data but does not reflect current realities and should not be viewed as establishing adjuvant RT as optimal care for current patients with potential high-risk features. Substantial stage migration is evident in the last 15 years, such that a greater fraction of patients are cured with surgery alone, even with adverse features such as extracapsular extension or seminal vesical invasion [9]. RT has developed such that higher doses are given to patients with prostate cancer, but with greater precision, so the outcomes might be better and patients will have fewer complications and a higher quality of life. The required study, as planned by the UK Medical Research Council, will examine adjuvant RT vs early salvage RT for endpoints of survival and avoidance of the use of hormonal therapy.

A delay in biochemical progression is one element in the requirement for adjuvant therapy to be beneficial, but it is not sufficient alone. If the same survival endpoint can be obtained with delayed treatment administered only to those who need it, the delayed treatment probably has an advantage. The absence of level-I data, i.e. a prospective, randomized controlled trial that examines the current practice of either adjuvant or early salvage RT, does not imply that we should extrapolate the results of one study, that was admittedly carried out well, but unfortunately had an insufficient primary endpoint and an inherently flawed study design.

CONFLICT OF INTEREST

None declared.

REFERENCES

- 1 Bolla M, Van Poppel H, Collette L *et al.* Postoperative radiotherapy after radical prostatectomy: a randomized controlled trial (EORTC Trial 22911). *Lancet* 2005; **366**: 572–8
- 2 Bolla M, Van Poppel H, Collette L, van der Kwast TH on behalf of EORTC Genito-Urinary and Radiation Oncology Groups. *ASCO 2007 Prostate Cancer Symposium*, Orlando, Florida, February 22–24, 2007
- 3 Wirth MP, See WA, McLeod DG *et al.* Bicalutamide 150 MG in addition to standard care in patients with localized or locally advanced prostate cancer. results from the second analysis of the early prostate cancer program at median follow up of 5.4 years. *J Urol* 2004; **172**: 1865–70
- 4 FDA Statement. Pfizer stops all torcetrapib clinical trials in interest of patient safety December 3, 2006 Available at <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01514.html> Accessed May 2007
- 5 Williams SD, Stablein DM, Einhorn LH *et al.* Immediate adjuvant chemotherapy versus observation with treatment at relapse in pathologic stage II testicular cancer. *N Eng J Med* 1987; **317**: 1433–8
- 6 Stephenson AJ, Shariat SF, Zelefsky MJ *et al.* salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA* 2004; **291**: 1325–32
- 7 Buskirk SJ, Pisansly TM, Schild SE *et al.* Salvage radiotherapy for isolated prostate specific antigen increase after radical prostatectomy. evaluation of prognostic factors and creation of a prognostic scoring system. *J Urol* 2006; **176**: 985–90
- 8 Thompson I, Tangen CM, Paradelo J *et al.* Adjuvant radiotherapy for pathologically advanced prostate cancer. *JAMA* 2006; **296**: 2329–35
- 9 Eggener SE, Roehl KA, Smith ND *et al.* Contemporary survival results and the role of radiation therapy in patients with node negative seminal vesicle invasion following radical prostatectomy. *J Urol* 2005; **173**: 1150–5

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INTRODUCTION

PSA screening for prostate cancer has been controversial since its introduction almost 20 years ago. Despite conflicting recommendations from professional societies, PSA has been widely adopted as a screening tool in the USA [1]. As a result, the incidence of prostate cancer has almost doubled; the lifetime risk of being diagnosed with prostate cancer in the USA is now 18% (SEER report, 1973–1995, available at <http://seer.cancer.gov/csr/1975-2004>); 90% of these men are currently diagnosed with early-stage disease, reflecting a significant stage migration [2] (<http://seer.cancer.gov/csr/1975-2004>). Proponents of screening have pointed to declining prostate cancer mortality rates over this period as evidence of the efficacy

of screening [3]. However, this trend has also been observed in regions where PSA screening is less prevalent, and others have cited improvements in therapy and earlier use of androgen-deprivation therapy as the cause of this decline [3–5]. The mortality data from two large trials evaluating PSA screening is expected within the next several years and, it is hoped, will resolve the question of whether PSA screening reduces mortality [6,7].

However, emerging data has served only to emphasize concerns regarding the suitability of PSA as a screening test. While the poor sensitivity of PSA leads to many missed cases of clinically significant prostate cancer, the rate of over-diagnosis, or detection of clinically insignificant prostate cancer, is thought to be more than 50% [8–11]. In