Radical Prostatectomy Outcome When Performed With PSA Above 20ng/ml

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Abstract
Many centres currently do not offer radical prostatectomy (RP) to men with high-risk localised prostate cancer due to concerns regarding poor outcome, despite evidence to the contrary. We identified 18 men undergoing RP with serum PSA >20ng/ml (high-risk by National Comprehensive Cancer Network definition) and minimum follow-up of 12 years (mean 13.5). Mean preoperative PSA was 37.0ng/ml (Range 21.1-94.0). Prostatectomy pathology reported extracapsular disease in 16 (88.9%), positive surgical margins in 15 (83%) and positive pelvic lymph nodes in 5 (27.8%). Overall and cancer-specific survival at 5 and 10-years was 83.3%, 88.2%, 72% and 76.5% respectively. With complete follow-up 11 (61.1%) are alive, and 5 (27.8%) avoided any adjuvant therapy. Complete continence (defined as no involuntary urine leakage and no use of pads) was achieved in 60%, with partial continence in the remainder. We conclude that surgery for this aggressive variant of localised prostate cancer can result in satisfactory outcome.

Introduction
Prostate cancer remains a leading cause of cancer-related death in Western society. Disappointingly a single optimal therapy for all cases of localised (i.e. without radiological evidence of metastasis) disease has not been established. Risk stratification systems for men with localised prostate cancer at diagnosis do exist, and universally a serum PSA >20ng/ml is considered one criteria constituting high-risk localised prostate cancer (HRLPC), inferring significant threat to life with an increased cancer-specific mortality. Concerns regarding poor oncologic outcome (failure to cure) and increased morbidity (particularly incontinence) have resulted in many urologists refusing to consider radical prostatectomy (RP) surgery in this setting, both in Ireland and abroad.

Most men with HRLPC are currently treated internationally with radiotherapy in combination with prolonged androgen-deprivation therapy, but the evidence for this treatment preference is weak. Published reports on the outcome of surgery for HRLPC do exist, albeit largely from very high-volume specialist centres which may not have applicability to general units in Ireland. In this report, we offer our experience of eighteen patients managed by RP within a single general unit in Dublin, with a PSA >20ng/ml at the time of surgery in the 1990s, and now each with a minimum of 12 years follow-up. RP was performed by one of two consultant urologists performing approximately 20 cases per year. For the purpose of this study, long-term oncologic outcome, need for adjuvant therapy, continence status and quality of life were assessed.

Methods
A complete single-centre database of 162 men undergoing RP between May 1990 and December 1998 allowed identification of all men with serum PSA>20ng/ml. Radiological evidence of metastasis and clinical locally advanced stage (ecT3) were contraindications to surgery. No case of "salvage" prostatectomy or neoadjuvant therapy was included. Reflecting the historical nature of this series, many men were diagnosed during this time by transperineal biopsies (TP), obsolete within our centre since 1998. The 2002 TNM staging system was retrospectively applied in each case. Decision to undertake RRP surgery during the period of this study was taken in the knowledge of a lack of any level-one evidence on this topic. All men were counselled in detail regarding alternative therapies (radiotherapy, hormonal manipulation or watchful waiting). Surgical technique was universally in a standard open retropubic manner described by Walsh and was not nerve-sparing. Pelvic lymphadenectomy (obturator fossa) was performed in all cases.

Histopathological analysis was by a single consultant pathologist with dedicated sub-specialised interest in urologic histopathology. Biochemical recurrence (BCR) was defined as PSA‡ 0.2 ng/ml on two consecutive occasions. In addition to review of medical records, all patients were contacted by telephone to garner specific information regarding urinary continence and quality of life. Complete (urinary) continence for the purpose of this study was defined as no need to use pads at any time by day or night in the last 6 months with no episodes of involuntary leakages of urine. Quality of life assessment was by telephone and was conducted without use of a standardized tool. Patients were simply asked to categorize their quality of life as good/excellent, fair or poor. Follow-up interval was defined as interval from surgery to time of last review, contact or correspondence. Information regarding date and cause of death was confirmed with the National Death Register. Any deceased patient with metastatic disease was deemed to have died from prostate cancer.

Statistical analysis was in a standard manner, and employed Fishers exact test for categorical variables, Mann Whitney test and Pearson Chi square test for parametric data. A scatterplot graph was produced for pre-operative PSA.
against cancer volume and analysed by Spearman Rank test. Kaplan Meier survival curves were produced for variables with significant influence on outcome. Multivariate analysis was undertaken in the form of Cox Regression Analysis. Any patient dying of any cause other than prostate cancer was included for analysis in the survivor group, as death would be from a competing outcome. Significance was universally defined as p<0.05.

Results
In total, 18 men (11.1% of men on database) with PSA>20ng/ml were identified. Transperineal biopsy technique provided the tissue diagnosis in 12. Pre-operative parameters (Table 1) and pathology of prostatectomy specimen (Table 2) are presented. Twelve men (66%) migrated to a higher Gleason score category (upgrade), and 16 men (89%) migrated to a locally-advanced T-stage (pT3; upstage). Evidence of metastatic disease within pelvic lymph nodes was found in 5 (27.8%). Positive surgical margin (PSM) was reported in 15 of the 16 men with pT3 disease, constituting 93.3% of the total group.

Outcome following surgery is detailed in Table 3. Death unrelated to prostate cancer was confined to a 66 year-old man who died as a result of myocardial infarction 9 months following his surgery (PSA was zero). Overall and cancer-specific survival at 5 and 10-years was calculated to be 83.3%, 88.2%, 72% and 76.5% respectively. BCR-free survival at 5 and 10-years was calculated to be 38.9% and 16.7%. Overall and disease-specific survival at 13.5 years is currently 61.1% and 64.7%. Five men with microscopic positive lymph nodes all received early adjuvant hormonal therapy, of which 3 have died from their disease (at 6, 7 and 11 years following surgery). Adjuvant therapy has included radiotherapy in 5 and androgen deprivation therapy in 13 men. Five men did not undergo any adjuvant therapy.

Statistical analysis demonstrated positive correlation between cancer volume and pre-operative PSA (p=0.016), but this may have been driven by a very high outlying cancer volume value. Seminal vesicle invasion (p=0.013) on pathologic analysis of RRP specimen was the only factor demonstrating statistical significance on univariate analysis. A Kaplan Meier curve is shown in Figure 1 for relationship between seminal vesicle invasion and survival (p=0.02; 95%CI 1.55-149.7).

Data regarding urinary continence and QOL was obtained from 10 men (excluded were the 7 deceased men and 1 man had moved abroad with family and was uncontactable). Six men fulfilled the definition for complete continence. Two further men used 1 or 2 pads per 24 hours, and the remaining 2 used multiple (>2) pads. QOL correlated with continence status, and all six with complete continence reported excellent or good QOL. One man using 1-2 pads per day also felt his QOL was excellent whilst 2 others reported fair QOL, and the remaining one man requiring multiple pads declared his QOL poor but had declined to undergo artificial urinary sphincter insertion by a colleague not involved in his prostate cancer surgery.

Discussion
Risk stratification for localised prostate cancer is now considered crucial as it allows men at greatest risk of death to avoid undertreatment, whilst men with least threat to their life may avoid the potential toxicity of any treatment. High risk cancer is the variant of localized disease that most commonly causes mortality, and has now been defined by the National Cancer Comprehensive Network (NCCN) in the US as diagnosis with a serum PSA >20ng/ml, clinical T-stage =/>3 (locally-advanced), or Gleason score =/>8 (high-grade).

Further refinement in stratification can result from pathologic analysis of the radical prostatectomy specimen and by later biochemical or clinical progress following therapy. Historically the majority of men with high risk disease have undergone radiotherapy in combination with hormonal therapy. This has not been based on evidence of efficacy derived from scientific trials (there are no completed prospective randomised trials), but rather has been based on 2 factors. Firstly, there has been concern about the efficaciousness of surgery, with most urologists admitting they are unlikely to cure these men with surgery alone. Secondly, substantial concerns have prevailed about the toxicity of surgery, largely urinary incontinence. Very good evidence now exists to cast major doubt over both these concerns.

Oncologic outcome for any malignancy is not defined simply by cure, but rather by survival, overall and disease-specific. It is quite possible that even if surgery does not cure many men with high risk disease, it...
Multimodal therapy for high risk localised prostate cancer, defined as radical surgery in all followed by radiotherapy in many and androgen-deprivation therapy in some, is an evolving unitary concept in the management of men with high risk localised disease. This approach represents the optimisation of the treatment strategy, and multi-disciplinary team consideration should be given to radical surgery in men presenting with this life-threatening variant of prostate cancer, at least when defined only by a PSA–>20ng/ml.

References
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