

Re: Radical Prostatectomy or Watchful Waiting in Prostate Cancer—29-Year Follow-up

Bill-Axelsson A, Holmberg L, Garmo H, et al

N Engl J Med 2018;379:2319–29

Experts' summary:

The 29-yr update of the SPCG-4 trial comparing radical prostatectomy (RP) with watchful waiting (WW) for prostate cancer (PC) gives some final answers to very old questions. By December 31, 2017, impressive numbers of 86/347 men in the RP arm and 56/348 men in the WW arm were still alive. PC-related deaths occurred in 71 versus 110 cases, and the RP group had gained a total of 2.9 extra yrs of life. The authors conclude that men with clinically detected, localized PC and long life expectancy benefit from RP.

Experts' comments:

We must keep in mind that the results represent intent-to-treat data that are diluted by a number of factors. In the RP group, 15% of patients did not actually undergo RP, including those for whom the operation was abandoned because of PC-involved lymph nodes. We now have good evidence that many of these patients would have benefited as well. In the WW group, 15% of protocol violators received a curative treatment. Furthermore, there was significant tumor-unrelated mortality within the first 10 yr of the trial, which also dilutes the results for the patient group of interest, namely those with high life expectancy. Of the patients randomized to WW at age <65 yr, almost 50% (81/166) finally developed distant metastases. Because of his higher life expectancy, a comparable patient seeking advice in 2020 can be predicted to draw an even higher benefit from RP.

On a more political level, reduction of PC-related mortality will become a more important focus of timely detection and treatment strategies. For many tumors, such as lung cancer, we are witnessing a dramatic reduction in mortality rates. PC threatens to become the only significant cancer with increasing instead of decreasing mortality numbers, predominantly because of demographic factors. Moreover, we must realize that most relevant answers concerning reduction of PC morbidity and mortality are given beyond year 15 of follow-up. Thanks to SPCG-4, robust answers are now available for RP versus WW. Similar data are not yet available for active surveillance, or for strategies that treat tumor foci instead of the tumor-bearing organ. Because of the long follow-up times, randomized controlled trials in PC are unavoidably more demanding than in most other malignant diseases, but without such trials, reliable answers never will become available and PC treatment will continue to be subject to myths and speculations.

Conflicts of interest: The author has nothing to disclose.

Michael Stöckle*

Department of Urology and Pediatric Urology, Saarland University,
Homburg/Saar, Germany

*Department of Urology and Pediatric Urology, Saarland University,
Kirrbergerstrasse, Homburg/Saar, Germany.
E-mail address: michael.stoeckle@uks.eu.

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**Re: Health Economic Analysis of Open and Robot-assisted Laparoscopic Surgery for Prostate Cancer Within the Prospective Multicentre LAPPRO Trial**

Forsmark A, Gehrman J, Angenete E, et al

Eur Urol 2018;74:816–24

Experts' summary:

Forsmark and co-workers performed a health economic analysis to assess how costs differed between robotic and open radical prostatectomy (RP) using data from the prospective nonrandomised multicentre LAPPRO trial [1]. A base-case analysis assuming 200 RPs per year per centre, a robot-system life expectancy of 7 yr, an annual discount rate of 3% on supply charges, and surgeon experience of >100 RPs was used to produce a reference scenario. Overall, 803 open (RRP) and 1835 robotic (RALP) RPs between 2008 and 2011 were analysed. RALP was associated with significantly lower postoperative sick leave, transfusions, reoperations, and readmissions.

After applying predefined costs for each resource variable, the authors found that RALP resulted in a higher cost per procedure of 3837 (95% confidence interval [CI] 2747–4928) purchasing power parity US dollars (PPP\$) compared to RRP ($p < 0.0001$). The difference in cost between the two approaches was affected primarily by

robot purchase/maintenance, sick leave, and operation time. Moreover, a post hoc analysis showed that a caseload of >400 RALP surgeries per year would lead to a substantial reduction in the cost difference compared to RRP (PPP\$ 1278, 95% CI 190–2746; $p < 0.001$). Conversely, inclusion of all the procedures irrespective of surgeon experience would lead to an increase in the cost difference between the two procedures.

Experts' comments:

In prospective studies, RALP showed no statistically significant improvement in continence and a small improvement in erectile function compared to open surgery, whereas surgeon experience seems to be the most important factor associated with optimal postoperative outcomes [2]. Nevertheless, there has been exponential diffusion of RALP worldwide in the past decade and urology patients are increasingly requesting a robotic approach. Surgical treatment of prostate cancer and of kidney cancer is increasingly performed via a robotic approach. Robotic urological surgery is not limited to the treatment of urological malignancies, and many other procedures are better when performed robotically. So the main question is how robotic systems can be made available to the entire population. The higher costs could represent a barrier for

policy makers in estimating health system performance. Forsmark et al showed that health costs were significantly higher for RALP compared to RRP. Their detailed analysis showed that operation time, robot purchase/maintenance, centre caseload, and surgeon experience are critical in reducing this cost difference. The results confirm a retrospective analysis of a representative US all-payer database in which costs were significantly higher for RALP compared to RRP, but were not significantly different among the highest-volume surgeons and hospitals [3]. Current evidence suggests that centralising surgical care in a few larger centres specialised in robotic surgery performed by very experienced surgeons can potentially optimise the quality of functional outcomes and increase the number of patients treated in the main facilities and treatment cost-effectiveness, leading to better utilisation of the equipment pool and new technologies and avoiding unnecessary duplication of infrastructure [4]. However, most larger centres are teaching hospitals and are involved in tutoring clinical fellows, which affects the time available for the high requirements of robotic surgery.

In our local context, the hub-and-spoke model was adopted in clinical practice in 2015. A single referral centre performs all robotic surgery for patients evaluated in the metropolitan area, including four district hospitals and the paediatric hospital. To obtain the most benefit from this collaboration, a modified hub-and-spoke system was adopted, in which not only patients but also previously trained surgeons move from the spokes to the hub. A twin robotic operating room is open 13 h/d from Monday to Saturday, with a median of six interventions (interquartile range 5–7) achieved per working day; a total of 1149 urological robotic procedures were performed in 2018 [5]. This system avoids the creation of A and B level surgeons, increases the inherent advantages of the standard system for patients, and increases the overall quality of the national health system.

Training of surgical fellows and surgeons from peripheral hospitals is possible with a very low impact on operating time and patient outcomes thanks to step-by-step tuition. This includes simulators and dry and wet laboratories in the first phase, followed by bedside assistance and modular training in robotic procedures.

The future promises a robotic revolution in urological surgery. Technologies will develop rapidly and it will be impossible to guarantee the highest quality technologies to every hospital. How can the robotic revolution be made available to the entire population? A modified hub-and-spoke model is the answer; this would lead to a higher surgical volume, meaning better patient outcomes, clinical research, and surgical training, as well as lower costs.

Conflicts of interest: The authors have nothing to disclose.

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Andrea Minervini^{a,*}, Andrea Mari^a, Riccardo Campi^{a,b}, Marco Carini^a
^aDepartment of Urology, University of Florence, Careggi Hospital, Florence, Italy

^bDepartment of Experimental and Clinical Medicine, University of Florence, Florence, Italy

*Corresponding author. Department of Urology, University of Florence, Careggi Hospital, San Luca Nuovo, Florence, Italy.
 E-mail address: andreamine@libero.it (A. Minervini).

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Re: A Prospective Adaptive Utility Trial to Validate Performance of a Novel Urine Exosome Gene Expression Assay to Predict High-grade Prostate Cancer in Patients with Prostate-specific Antigen 2–10 ng/ml at Initial Biopsy

McKiernan J, Donovan MJ, Margolis E, et al.,

Eur Urol 2018;74:731–8

Experts' summary:

McKiernan et al report a prospective, multisite validation of the ExoDx Prostate IntelliScore (EPI) test, which is a urine-based three-gene exosome expression assay, using a cohort of 503 men aged >50 yr with prostate-specific

antigen (PSA) of 2–10 ng/ml at initial prostate biopsy. The EPI test was superior to a standard of care (SOC) model (PSA level, age, race, and family history), with an area under the receiver operating characteristics curve (AUC) of 0.70 compared with 0.62 for the SOC model. Use of the prespecified cutoff point of 15.6 (defined in the previous study and recommended for the second utility phase) would avoid 20% of total biopsies at a cost of missing 7% of high-grade prostate cancers (PCs). The results of the study correspond well to the previous prospective data [1] and demonstrate that the EPI test is predictive of high-grade PC at initial biopsy and contributes to reducing unnecessary prostate biopsies.