Thromboembolic Complications in 3,544 Patients Undergoing Radical Prostatectomy with or without Lymph Node Dissection

Stavros I. Tyritzis,* Anna Wallerstedt, Gunnar Steineck, Tommy Nyberg, Jonas Hugosson, Anders Bjartell, Ulrica Wilderäng, Thordis Thorsteinsdottir, Stefan Carlsson, Johan Stranne, Eva Haglind and Nils Peter Wiklund on behalf of the LAPPRO Steering Committee†

From the Section of Urology, Department of Molecular Medicine and Surgery (SIT, AW, SC, NPW) and Division of Clinical Cancer Epidemiology (GS, TN), Karolinska Institutet, Stockholm, Division of Clinical Cancer Epidemiology (GS, UW, TT) and Departments of Urology (JH, JS) and Surgery (EH), Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Department of Urology, Skåne University Hospital (AB), Malmö and Department of Oncology, Lund University (AB), Lund, Sweden, Center for Minimally Invasive Urological Surgery, Athens Medical Center (SIT), Athens, Greece, and Faculty of Nursing, University of Iceland (TT), Reykjavik, Iceland

Purpose: Lymph node dissection in patients with prostate cancer may increase complications. An association of lymph node dissection with thromboembolic events was suggested. We compared the incidence and investigated predictors of deep venous thrombosis and pulmonary embolism among other complications in patients who did or did not undergo lymph node dissection during open and robot-assisted laparoscopic radical prostatectomy.

Materials and Methods: Included in study were 3,544 patients between 2008 and 2011. The cohort was derived from LAPPRO, a multicenter, prospective, controlled trial. Data on adverse events were extracted from patient completed questionnaires. Our primary study outcome was the prevalence of deep venous thrombosis and/or pulmonary embolism. Secondary outcomes were other types of 90-day adverse events and causes of hospital readmission.

Results: Lymph node dissection was performed in 547 patients (15.4%). It was associated with eightfold and sixfold greater risk of deep venous thrombosis and pulmonary embolism events compared to that in patients without lymph node dissection (RR 7.80, 95% CI 3.51–17.32 and 6.29, 95% CI 2.11–18.73, respectively). Factors predictive of thromboembolic events included a history of thrombosis, pT4 stage and Gleason score 8 or greater. Open radical prostatectomy and lymph node dissection carried a higher risk of deep venous thrombosis and/or pulmonary embolism than robot-assisted laparoscopic radical prostatectomy (RR 12.67, 95% CI 5.05–31.77 vs 7.52, 95% CI 2.84–19.88). In patients without lymph node dissection open radical prostatectomy increased the thromboembolic risk 3.8-fold (95% CI 1.42–9.99) compared to robot-assisted

Abbreviations and Acronyms

DVT = deep venous thrombosis

LAPPRO = Laparoscopic Prostatectomy Robot Open

LND = lymph node dissection

LRP = laparoscopic radical prostatectomy

ORP = open radical prostatectomy

PE = pulmonary embolism

RARP = robot-assisted laparoscopic radical prostatectomy

Accepted for publication August 15, 2014.

Study received Gothenburg regional ethical review board approval.

Supported by the European Urological Association European Urological Scholarship Program 2012-2013 (SIT).

* Correspondence: Section of Urology, Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden (telephone: + 46 76 25 83 802; FAX: +46 8 517 735 99; e-mail: stavros.tyritzis.2@ki.se).

† Eva Haglind, Principal Investigator; Gunnar Steineck, Deputy Principal Investigator; Bo Anderberg, Department of Surgery, St. Görans Hospital and Ingela Björholt, Nordic Health Economics, Göteborg; Thomas Jiborn, Department of Urology, Skåne University Hospital and Lund University; Jan-Erik Damber and Ali Khatami, Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg; Mikael Wulkner-Sylmé, Department of Urology, Varberg Hospital; Christer Edlund, Department of Surgery, Kungsbacka Hospital; Erik Pileblad, Capio Lundby Hospital; Hans Boman, Department of Surgery, Alingsås Hospital; Ola Bratt, Department of Urology, Helsingborg Hospital; and Ulrika Westlund, Department of Urology, Södersjukhuset.

0022-5347/15/1931-0117/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2014.08.091
Vol. 193, 117-125, January 2015
Printed in U.S.A.

laparoscopic radical prostatectomy. Lymph node dissection induced more wound, respiratory, cardiovascular and neuromusculoskeletal events. It also caused more readmissions than no lymph node dissection (14.6% vs 6.3%).

Conclusions: Among other adverse events we found that lymph node dissection during radical prostatectomy increased the incidence of deep venous thrombosis and pulmonary embolism. Open surgery increased the risks more than robot-assisted surgery. This was most prominent in patients who were not treated with lymph node dissection.

Key Words: prostate, prostatectomy, lymph node excision, venous thrombosis, pulmonary embolism

"PRIMUM, non nocere" means "First, do no harm," as Hippocrates proclaimed 25 centuries ago. When it comes to LND during radical prostatectomy, the famous quote becomes more apparent since balancing the benefits and risks of this procedure (survival on one side of the scale and patient morbidity on the other) is still a subject of research.[1,2]

The rates of PE and DVT after LND in various studies of ORP and RARP fluctuate between 0.2% and 8.0%[1] even in the era of improved surgical technique, external compression devices, stockings, early patient mobilization and aggressive heparin administration. Notably 20 years ago the rates were threefold to eightfold higher. However, groups suggest that LND does not increase the incidence of thrombosis and so they do not administer heparin, regarding this as an unnecessary precaution.[3–5]

The mortality rate in patients who experience a thromboembolic event after radical prostatectomy is disturbing, reaching an incidence of 3%.[6] Thus, the absence of thromboembolic events is considered one of the most important quality indicators of surgery.[6] Additionally, the issue of thromboembolic events and pharmacological prophylaxis was introduced in 2012 by the Pasadena Consensus Panel for prostate cancer as a matter of high priority for research.[7] Nevertheless, we do not know to what extent LND increases the risk of thrombosis during radical prostatectomy or the best ways to prevent it.

We investigated the association of LND with increased postoperative morbidity and the incidence of thromboembolic events by comparing patients treated with ORP or RARP with or without LND using the large cohort of the LAPPRO trial.

PATIENTS AND METHODS

The study population was derived from LAPPRO, a prospective, controlled clinical trial comparing ORP and RARP.[8] In Sweden 14 urological departments participated, including 7 where ORP was done and 7 where RARP was done transperitoneally. The study was approved by the Gothenburg regional ethical review board and the trial is registered in the Current Controlled Trials database (ISRCTN06393679). The LAPPRO study was designed with urinary incontinence as the primary end point. Thromboembolic complications were the tertiary outcomes investigated in the current secondary substudy.

LAPPRO inclusion criteria were TNM stage T1-T3 prostate cancer, no clinical sign of metastatic disease, PSA 20 ng/ml or less, age 75 years or less, no previous malignancy, fitness for prostatectomy, informed consent, and ability to read and write Swedish. Our followup end point for reporting postoperative adverse events and hospital readmissions was 12 weeks.

Data were prospectively collected by a neutral third party. Health care personnel and patients completed validated clinical record forms and questionnaires, respectively, preoperatively and 3 months postoperatively. The questionnaires were tested and validated face to face by experts and prostate cancer survivors. Analysis was based on patient reported outcomes of adverse events and patient reported reasons for hospital readmission.

All information was manually entered in a secured electronic data set. Several efforts were made toward the quality assurance of collected data. Approximately 1% of the data was reentered in the database and cross checked.

Statistics

Data were entered in EpiData 3.1 (http://www.epidata.dk/) and exported to SAS® 9.2 for statistical analysis. We performed exploratory variable selection with the aim of identifying those of the possible known confounders that were most strongly associated with the outcome of DVT and/or PE. To do this we used successive formation of logistic regression models (forward selection with the inclusion criterion $p < 0.10$). Table 1 shows the association between combinations of surgical approach and LND status, and the DVT and/or PE outcome unadjusted and adjusted for identified possible confounders.

LND Technique

Participating surgeons performed limited or extended LND. Extended LND was done in most patients with high risk disease according to the D'Amico tables.[9] Extended LND included removal of the nodes overlying the external iliac artery and vein, nodes in the obturator fossa located cranial and caudal to the obturator nerve, and nodes medial and (at some centers) lateral to the internal iliac artery. Limited LND included only the obturator nodes.

In all patients postoperative care consisted of rapid ambulation (the evening of operation), stockings and low molecular weight heparin. Heparin administration patterns were grouped into 2 categories, including low dose—5,000 U for 5 to 7 days and high dose—5,000 U for