

Comparison of B lymphocyte effects of laparoscopic versus open prostatectomy in prostate cancer patients.

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Abstract

The preoperative B-cell counts (CD 19+) appeared to be more reduced by laparoscopic prostatectomy when compared with open surgery. These findings are important because accumulating evidence suggest that the B-cell subsets emerged in response to prostate cancer exhibit association with unfavorable prognosis. High per cent of B- cells infiltrating tumor were shown to be associated with more aggressive disease. The B-cell depleting therapies used with different prostatectomy settings should be closely monitored to make timely adjustments to peripheral CD19+ counts.

Introduction

Prostate cancer (PCa) is the most common cancer among men and the second leading cause of male cancer deaths in developed countries (1). A significant number of men develop prostate cancer recurrence within 10 years following surgical treatment. Further therapies are needed to improve survival in men in postoperative period. In prostate cancer, effective immune strategies capable to improve therapeutic outcomes were extensively investigated (2). The immune checkpoint inhibitors (3), vaccines (4,5) or B lymphocyte depleting compounds (6,7) are an example of innovative tactics capable to improve therapeutic outcomes and to reduce side effects. However, application of immunotherapy might be straightforwardly dependent on the immune competence of a recipient. Interestingly, the surgical procedure itself – open vs laparoscopic appeared to elicit significant rearrangements of the immune system in various

surgical settings (8,9,10). Laparoscopic radical prostatectomy (LRP) has been increasingly adopted by urologists for treating patients with prostate cancer (PCa). It has several short-term advantages, such as a quicker recovery, less pain, shorter hospitalization time, and lower blood transfusion rate. However, there is no high-quality evidence to identify the comparative effectiveness of LRP versus open radical prostatectomy (ORP) for oncological outcomes (11). Thus, the higher cost of an LRP procedure might seem to be a disadvantage. The objective of this study was to compare two surgical methods focusing on immune dysfunction induced by radical prostatectomy (RP) stress.

Methods

One hundred and eight consecutive patients undergoing either LRP or ORP were included in the study to assess their immune and inflammatory responses. All participants provided written informed consent with guarantees of confidentiality and study was approved by institutional Bioethics Board. The mean age and prostate specific antigen (PSA) value of the participants were 62.5 years and 9.0 ng/mL respectively. The participants in LRP and ORP groups were selected to represent homogeneous characteristics by preoperative PSA, age, Gleason score, pathological stage (pT2 or pT3), positive margins, and preoperative T - and B - lymphocyte counts. Blood samples were collected before surgery, then on day 30 and day 91 after surgery, and all were assayed for CD19+ and CD3+. The LRP extraperitoneal prostatectomy was performed using a five-trocar technique. The prostato-vesical junction was incised and the vas deferens and seminal vesicles were dissected. The prostate was dissected in an antegrade fashion. The urethra was transected following a separation of dorsal venous complex. Running suture vesicourethral anastomosis was placed. Conventional open radical retropubic prostatectomy was performed extraperitoneally in a retrograde fashion following dissection of the urethra. The urethro-vesical anastomosis sutures used an interrupted stitch. Propofol total intravenous anesthesia without sevoflurane or opioid was applied to all study participants. Patient follow-up included PSA measurements every 3 months for two years and then every 6 months. Progression free survival (PFS) was defined as the time to any progression (biochemical recurrence or radiological).

Results

There was no statistical difference in the PFS of patients between the two surgical methods ($p = 0.4$, Fig 1c). Unexpectedly, the surgical procedure itself was triggering a decline in circulating B cell counts during the early postoperative stage (days 30 – 91). The effect was seen in the group of patients operated predominantly using the LRP method. The gap between LRP and ORP groups was gradually increasing and observable for three months postoperatively (Fig 1). No effect was seen with CD3+ cells. The CD19+ lymphocytes (Fig 1a), unlike CD3+ (Fig 1b), exhibited diverse response patterns in patients operated on using ORP vs LRP at the 30 day and 91-day time point postoperatively. For LRP: pre-RP vs day 30 was statistically significant ($p < 0.05$); for ORP: pre-RP vs day 91 did not differ ($p = 0.3$); also day 30 vs day 91 ($p = 0.1$).

Cumulative PFS (Kaplan-Meier) were comparable between ORP and LRP groups; log-rank $p=0.4$ (Fig 1c).

Discussion

The importance of these changes for postoperative immune function are unknown. Short-lived B cell decline on day 5 or day 1 was observed by others in laparoscopic but not open method of colorectal surgery (8) or gynecological surgery (9). The B cell effect specifically in PCa patients might have several important implications. The intratumoral B cell infiltration and B cell involvement in PCa progression are prevailing (12). Depletion of circulatory B cell by rituximab appeared to elicit a sustainable remission at least in two reported PCa cases with metastatic disease (13,14). A phase I clinical trial evaluating rituximab as neoadjuvant therapy in patients prior to radical prostatectomy is currently ongoing (15) as well as several clinical trials including PCa surgical or adjuvant treatment with immune checkpoint inhibitors (ICI) (16). The surface of B cells contains PD-1 and CTLA4, implying that the ICI could target B lymphocytes as well (17). Recently PCa was shown to induce monoclonal B-lymphocytosis with a specific immunophenotype (mostly CD19+CD5+) resembling chronic lymphocytic leukemia (18). We also observed an increase in preoperative CD19+ counts predominantly in poor prognosis patients. The specific subset of B cells which was declining postoperatively is to be elucidated. It might be unique and different from a CD19+CD5+ clone requiring further investigation. It could explain why rituximab is only efficient in a fraction of patients. Unlike normal B-lymphocytes, these atypical B-monoclonal cells appeared to be significantly more resistant to radiation therapy (18). In some studies, LRP was shown to exhibit less tumor cell spillage, less inflammatory effects, and less clotting dysfunction as compared to ORP. Specific LRP impact on CD19+ cells might be additional evidence in the comparative effectiveness of the two methods. We assume that the clinical trials exploring perioperative B-cell depletion (rituximab, ibrutinib) or B-cell modulation (ipilimumab, pembrolizumab) should consider the impact of the surgical method applied.

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Conflict of Interest None declared

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Authors' contributions PB and GZ participated in the study design and drafted the manuscript. ND performed flow cytometry subset analysis. PB gathered patient's follow-up results and carried out statistical analysis. ABH, FJ and VP conceived the study and helped to revise the manuscript. All authors read and approved the final manuscript.

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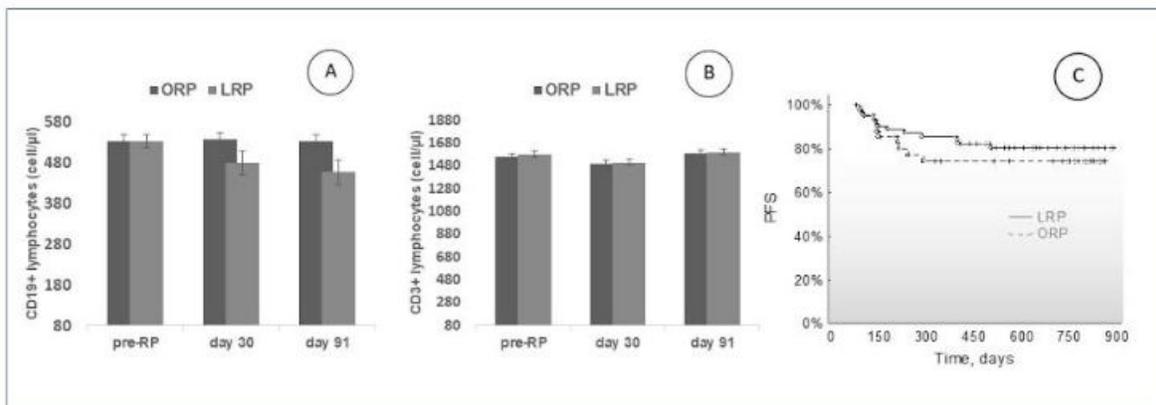


Fig 1. B-lymphocyte vs T- lymphocyte response in laparoscopic (LPR) and open (OPR) radical prostatectomy patients.