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Opinion

Level 1 Evidence for Robotic Surgery for Urological and Gynecological Pelvic Cancers: Where do We Currently Stand?

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Abstract

Robotic surgery is used for the surgical removal of female pelvic malignancies and encompasses procedures as radical cystectomy and radical hysterectomy. The aim of this paper is to provide an update of level 1 literature evidence about the outcomes of robotic surgery compared to other surgical approaches for the treatment of bladder, endometrial and cervical cancer. A non- systematic search of the PubMed and Scopus databases was conducted to identify peer-reviewed randomized controlled trials (RCTs) comparing surgical approaches for radical cystectomy and hysterectomy. To the purpose of capturing the lastest updates, 2020–2022 literature was reviewed. In the field of radical cystectomy, two RCTs supported the implementation of robotics as a more beneficial approach than open surgery - in terms of faster recovery, less thromboembolic events, less infectious events. In gynecology, despite robotics is accepted for the treatment of early endometrial tumors, the role of minimally invasive surgery (MIS) for the treatment of cervical cancer is still debated, with two recent systematic reviews and meta-analyses reporting conflicting results. Two- decades after the introduction of robotic surgery, there is still a number of current studies evaluating its role for the treatment of urological pelvic malignancies, especially for bladder cancer. The role of robotic surgery alone for the treatment of gynecological malignancies has been scarcely addressed with robotics being mostly evaluated as a part of MIS; updates about MIS for the treatment of cervical cancer continue to be ongoing.

Keywords: robotic surgery; randomized controlled trial; pelvic cancer; prostate cancer; bladder cancer; endometrial cancer; cervical cancer

1. Introduction

Robotic surgery represents a step towards innovation and precision for oncological and reconstructive surgery. Technical advantages of robotics include a stable 3D vision with a camera that can constantly be adjusted by the surgeon; an extended range of motion of the instruments and better ergonomics that may overcome the drawbacks of laparoscopy in complex cases and in narrow operative fields such as the pelvis. Actually, robotic surgery applies to all procedures requiring a precise dissection and/or complex reconstruction and is useful in anatomical sites far-off to be reached, such as male and female pelvis [1].

Robotic surgery has been used for the surgical removal of pelvic malignancies, including prostate cancer, bladder cancer, endometrial cancer, and cervical tumors [1,2].

The aim of this narrative review is to provide an update of the highest-level literature evidence dealing with the outcomes of robotic surgery compared to other surgical approaches, namely pure laparoscopy and open surgery. An overview of articles published in 2020 and 2022 was performed for robotic radical cystectomy (RARC) and robotic hysterectomy (RH).

2. Methods

A non-systematic search of the PubMed and Scopus databases was conducted to identify peer-reviewed randomized controlled trials (RCTs) comparing surgical approaches for radical cystectomy and radical hysterectomy. To the purpose of capturing the lastest updates, 2020–2022 literature was reviewed.

Inclusion Criteria

Only English-language publications were included in this study. The following keywords were used "robot", "robotic", "randomized controlled trial", "RCT", "radical cystectomy", "radical hysterectomy". Meta-analyses were included when appropriate. Abstract reviews were conducted to determine the articles' relevance for the review aims. Full-text analysis of all relevant English-language original articles was subsequently performed by one author (MCS) and summarized after discussion with an independent third party (AE). No formal quality assessment of the included studies was conducted.

3. Results

After two-decades of routinely use of robotic surgery, there are still plenty of current studies evaluating the role of robotic surgery for the treatment of pelvic malignancies, some of them comparing robotics to different surgical approaches.

3.1 Robotic Radical Cystectomy

Radical cystectomy (RC) has been widely investigated during the recent years [3]. Overall, 3 RCTs and an update of a previous RCT were published within 2020–2022 time frame [4–8]. RC represents a complex surgical intervention for the treatment of muscle invasive (MIBC) or high-risk non-muscle invasive bladder cancer (NMIBC), made up from both a dissection (RC and nodal dissection) and a reconstructive step (urinary diversion). The safety of robotic surgery for urothelial cancer has been initially questioned because of the suspicion of atypical recurrences after RARC due to peritoneal seeding; therefore, previous RCTs focused mostly on oncological outcomes of the robotic approach. One of the most important trials was the RAZOR (2018) that stated the non-inferiority of RARC compared to the open approach in terms of 2-years progression free survival and other oncological outcomes [3]. Peri-operative adverse events were similar between approaches; thus, beyond the safety of RARC, the study failed to demonstrate an advantage of robotics over the open approach. An update of the RAZOR trial was published in 2020 and analyzed QoL (quality of life) items through the Functional Assessment of Cancer Therapy (FACT)-Vanderbilt Cystectomy index subscale and the Short Form 8 Health Survey (SF-8); once more the trial showed the lack of any significant difference in health related QoL between robotic and open cystectomies [4]. Another update of a previous RCT (CORAL (Cystectomy Open Robotic and Laparoscopic) Trial) was published in 2020: the study addressed long-term oncological outcomes of 60 patients previously randomized to receive RARC, laparoscopic, or open surgery for the treatment of MIBC or high-risk NMIBC. At 5-years, recurrence-free survival (RFS) was 58%, 71% and 60% and cancer-specific survival (CSS) was 68%, 69% and 64%, respectively [5]. Despite the small sample size, the conclusion was that there was no difference in oncological endpoints at 5-years between surgical approaches. From these studies and other prospective multicentric experiences, robotic surgery is currently considered equivalent to open surgery as far as oncological outcomes are concerned [2,5].

In 2022, two more RCTs have been published to evaluate if robotic surgery is superior to open surgery in terms of peri-operative results. As stated, the RAZOR (Robot-assisted *vs.* Open radical) trial failed to demonstrate a clear advantage of robotic surgery in terms of surgical outcomes. However, both the RAZOR and CORAL trial enrolled RARC with extracorporeal reconfiguration of urinary diversions (UD) and it has been argued that a mini-laparotomic approach may mitigate the advantages of robotic surgery — i.e., absence of peritoneum exposure and improved tissue handling. Mastroianni *et al.* [6], designed a RCT to demonstrate the superiority of RARC with intracorporeal UD in terms of 50% transfusion rate reduction. By randomizing 116 patients (58 RARC, 58 open surgeries), overall peri-operative transfusion rates were significantly lower in the RARC cohort (22%) compared to the open one (41%). When addressing patient related QoL on a subset of patients with 1-year follow up, an equivalence between approaches for most of QoL domains was evident [7]. Another recent RCT comparing peri-and post-operative outcomes of robotic and open surgery for RC was recently released, the iROC (Robotically Assisted Radical Cystectomy with Open Radical Cystectomy) trial [8]. By including 317 patients who underwent either robotic or open RC, those undergoing RARC with complete intracorporeal UD demonstrated superiority in terms of primary outcomes – number of days alive and out of the hospital within 90 days of surgery; moreover, when investigating secondary endpoints, RARC with intracorporeal UD was also able to reduce thromboembolic complications (1.9% *vs.* 8.3%) and wound complications (5.6% *vs.* 16.0%). The QoL items were better for RARC patients at 5 weeks whereas disability scores - investigated with the World Health Organization Disability Assessment Schedule 2.0 — were improved at 5 and 12 weeks within the robotic arm. Cancer recurrence and overall mortality were similar between groups [8].

In conclusion, recent level 1 evidences confirmed the safety of robotic surgery by ruling out the risk of increased cancer recurrence rates; meanwhile, the superiority of the robotic approach with the intracorporeal reconfiguration of UD have been confirmed within two concurrent 2022 RCTs.

3.2 Robotic Hysterectomy

Robotic surgery for the treatment of endometrial cancer has been investigated during the last decade [9,10]. Despite some controversies arising from recent retrospective studies [11,12], minimally invasive approach continues to be the preferred surgical approach for early stage endometrial carcinoma (I/II) according to the ESGO/ESTRO/ESP Guidelines, with total hysterectomy and bilateral salpingo-

oophorectomy being recommended [13].

The role of robotic surgery for the treatment of cervical cancer is still under investigation and the recent literature continues to display conflicting results. As known, the safety of robotic surgery for the treatment of early cervical cancer has been questioned after the publication of the results from phase 3 multicenter RCT by Ramirez *et al.* [14] in 2018 (LACC trial) that randomized 631 patients to receive either minimally invasive surgery (MIS) (319 patients, 84.4% laparoscopic and 15.6% robotic procedures) or open surgery (312) for IA1, IA2 or IB1 stage cervical cancer. At 4.5 years, MIS patients had lower rates of disease-free survival (DFS) compared to patients who underwent open surgery (86% *vs.* 96.5%) and lower rates of overall survival (93.8% *vs.* 99.0% at 3-years) [14]. Secondary outcomes of the LACC trial were published in 2020 and focused on the incidence of adverse events in MIS compared to open radical hysterectomy. When categorized and graded with the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0 (CTCAE), MIS resulted in similar rates of adverse events compared to open surgery [15]. The finding was consistent across intra- and post-operative courses for grade 2+ adverse events. The role of MIS with regards to peri-operative outcomes was investigated in a recent systematic review and meta-analysis by Li *et al.* [16]: by including 39 non-randomized studies and 1 RCT. The authors found that MIS is superior to laparotomy in terms of fewer post-operative complications (wound infection, pelvic infection and abscesses, lymphedema, intestinal obstruction, pulmonary embolism, and urinary tract infection) but is associated with a higher degree of intra-operative aggregate complications (cystotomy, bowel injury and subcutaneous emphysema) and post-operative fistula complications. However, when addressing the comparison between robotic alone and open surgery in a subgroup analysis, RH displayed a reduced risk of post-operative complications compared to laparotomy (odds ratio (OR) 0.42, 95% confidence interval (CI) 0.26–0.68, $p < 0.01$) and similar risk of aggregate intra-operative complications (OR 1.11, 95% CI 0.62–2.01, $p = 0.11$) [16].

Another systematic review and network meta-analysis was released in 2022 by Guo *et al.* [17], evaluating the outcomes of different surgical approaches to radical hysterectomy for cervical cancer. Thirty studies — including observational ones with survival analysis — accounting for more than 11,000 patients were evaluated and robotic surgery was confirmed to provide the lowest degree of blood loss [17]. Twenty studies compared the length of stay among different approaches and RH was associated with shorter hospitalization together with laparoscopy. Beyond stating superior results for robotics in terms of peri-operative course, the same paper found similar oncological outcomes among surgical approaches, in terms of both survival and tumor recurrence rates [17].

Opposite to the results from Guo [14], Zhang *et al.* [18] reported poorer survival outcomes for MIS. By performing a systematic search of the literature and a meta-analysis of 48 studies involving 23,346 patients, Zhang *et al.* [18] found poorer 3-year DFS rate for MIS compared to open surgery (hazard ratio (HR) 1.08, 95% CI 1.01–1.16, $p = 0.031$), without significant difference in medium-term outcomes of survival (OS) as well as long term (5-year) DFS and OS. A 5-year difference in DFS was evident when stratifying patients by tumor volume, with poorer survival outcomes for tumors more than 2 cm in size (HR 1.65, $p = 0.041$) [18]. A subgroup analysis about the direct comparison between robotic and open surgery was not performed, and only 15.6% (3653/23,346) of the patients included in this meta-analysis underwent robotic surgery.

Further prospective studies are required to address this issue [19]. Patients' selection and surgical strategy may play a key role to improve the safety of MIS in the field of cervical cancer; the application of proper oncological surgical principles — such as avoidance of transcervical uterine manipulators, cervical and tumor containment prior to colpotomy — should be pursued when dealing with robotic surgery for cervical cancer [19].

Recent literature is lacking RCTs about ovarian cancer within the 2020–2022 time frame. The only published article is a post-hoc analysis of the STELLA-2 trial. The previous STELLA trial compared two surgical techniques (extraperitoneal *vs.* transperitoneal) of aortic lymphadenectomy for surgical staging of endometrial and ovarian cancer [20]. The update from Bebia *et al.* [21], found that in a subgroup of patients robotically-treated, the rate of surgical complication was lower than those occurring in a laparoscopic group. Nodal retrieval, operative time and LOS were similar between groups, thus the authors favored the robotic approach for its 3D visualization, ergonomics and precision.

4. Conclusions

The current overview of the 2020–2022 literature displays plenty of recent findings about robotic surgery for the treatment of uro-gynecological pelvic malignancies. The implementation of robotics as a beneficial approach to radical cystectomy has been supported by the publication of recent RCTs. Despite robotic surgery is widely accepted for the treatment of endometrial tumors, further studies are required to highlight its role for cervical cancer, with improvement likely to derive by the optimization of surgical strategy and patient selection.

Author Contributions

MCS, GGai and BR conceived the topic of this paper; being this an expert opinion, all authors have contributed to the contents. MA, SA, LS, ST and TC drafted the paper; AE, GGar, MS, PPG, AM, MF and SM supervised the opinion round and provided scientific insights. All authors

read and approved the final manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest. GGai is serving as one of the Guest editors of this journal. AM is serving as one of the Editorial Board members and Guest editors of this journal. We declare that GGai and AM had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to MHD.

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