Research Progress of Survival Outcomes in Early-Stage Cervical Cancer Patients Undergoing Robotic Radical Hysterectomy

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Abstract: Minimally invasive surgical (MIS) for early-stage cervical cancer (ECC) has been controversial following the publication of The LACC trial. However, MIS consists of traditional laparoscopic surgery and robotic-assisted laparoscopic surgery. The aim of this article is to discuss the research progress of ECC undergoing robotic radical hysterectomy (RRH) with a view to providing more surgical options for patients.

Keywords: Early-Stage Cervical Cancer; Robotic Radical Hysterectomy; Survival Outcomes

Introduction

Cervical cancer is the fourth malignancy of women, with 300,000 death worldwide in 2018 [1]. With the widespread availability of human papilloma virus (HPV) vaccination and cervical cancer screening, more patients have been diagnosed at an early stage and the proportion of ECC is on the rise per year.

The standard treatment for ECC is radical hysterectomy (RH) plus pelvic lymph node dissection. ECC is defined as stage IA-IB1 and optionally stage IIA1 according to the FIGO 2009 staging [2]. Until the pioneering of laparoscopic techniques in the early 1990s, open surgery was the standard procedure for ECC [3-4]. MIS including traditional laparoscopic techniques and robot-assisted laparoscopic techniques has developed rapidly over the past 20 years. Previous studies had reported that MIS was associated with less operative time, lower estimated intraoperative bleeding, and fewer intraoperative and postoperative complications than ARH, and the long-term oncology outcomes are not inferior to open [5-8]. However, a prospective randomized controlled trial published in the New England Journal in 2018 produced alarming results. The LACC trial [9] noted that MIS led to lower 3-year disease-free survival (DFS) and lower 3-year overall survival (OS). A large cohort study including 2,461 patients reached similar conclusions. These two high-quality studies called into question the use of MIS in ECC, and even subsequent NCCN guidelines recommended open surgery as the standard procedure for patients with ECC.

However, in the LACC trial, only 15.6% of patients in the MIS group underwent RRH. It is well known that the robotic laparoscopic platform was developed to address the limitations of conventional laparoscopic surgery by providing a clearer 3D view, performing tremor filtering of surgical instruments, and using robotic arms to perform more delicate operations that cannot be performed manually. Based on this, the author summarized the research progress in ECC undergoing RRH, with a view to providing more surgical options for ECC patients.

1. The controversy of ECC undergoing MIS

Previous studies had reported no difference in long-term oncology outcomes between LRH and ARH. Bogani *et al*. performed a propensity-matched analysis of 65 pairs of patients who underwent LRH or ARH and showed no statistical difference in 5-year DFS and OS [10]. In addition, Wang *et al*. conducted a retrospective study of patients with stage Ia2-IIa2 cervical cancer who underwent LRH and ARH and matched the two groups according to risk factors for recurrence. Their

survival analysis showed no significant difference in recurrence rates between the two groups. The 5-year DFS and OS were without difference [11], and LRH had a lower rate of postoperative complications.

The publication of the LACC trial shattered this calm, in which patients were randomly allocated to either the MIS group (n=319) (LRH or RRH) or ARH group (n=312), with a DFS at 4.5 years of 86.0% in the MIS group and 96.5% in ARH group. MIS was associated with a lower 3-year DFS (91.2% vs. 97.1%), a difference that persisted after adjusting for age, body mass index (BMI), staging, LVSI, and lymph node involvement. MIS was also associated with a lower 3-year OS (93.8% vs. 99.0%). Individual countries subsequently reported their data. The SUCCOR study in Europe reported by Chiva *et al.* [12] was a multi-center, retrospective, observational cohort study that included 693 patients who underwent MIS or ARH. Their results showed that MIS increased the risk of recurrent death, but when patients underwent MIS with protective vaginal closure, the recurrence rate was similar to that of ARH.

2. The research progress of ECC undergoing RRH

The DaVinci robotic surgical system was first described by Sert and Abeler in 2006 [13]. It inherits the advantages of laparoscopy, but is superior to it in that 1) 3D high-definition imaging technology; 2) simulated wrist surgical instruments eliminate chatter; 3) the robotic hand has greater dexterity, accuracy, and freedom of movement, enabling fine manipulation in confined spaces. Robotic surgery was originally introduced with the expectation that it would prove optimal and evolve to eventually replace conventional laparoscopic surgery [14]. Some relevant studies have also confirmed that RRH has lower intraoperative bleeding, shorter hospital stays, lower rates of wound-related complications, and postoperative fever-related complications than LRH in terms of comparative intraoperative and short-term postoperative outcomes.

Alfonzo [15] *et al.* conducted a Swedish national population-based cohort study that included 864 patients (236 ARH, 628 RRH) with stage IA1-IB cervical cancer who underwent RRH, and 5-year OS in the ARH and RRH groups were 92% and 94%, and 5-year DFS of 84% and 88%, respectively, with similar patterns of recurrence in both groups. Using propensity score analysis, 232 patients were included in each group and there was no difference in survival between the two groups. Similarly, Jensen [16] *et al.* reached a similar conclusion for Danish population-based data. Falconer [17] *et al.* performed follow-up statistics on patients who received RRH at their referral hospital, with a median follow-up time of 52 months, a recurrence rate of 5.6%, a 4.5-year PFS of 93.1%, and a 4.5-year OS was 95.1%. When stratified by tumor diameter, patients with tumors >2 cm had a worse PFS ($p = 0.01$), and there were no statistically significant for OS. A meta of 26 studies comparing RRH and ARH showed that RRH had better perioperative numbers [18].

3. Looking forward

The results of the LACC trial have been widely discussed. However, shortcomings regarding its study are also noteworthy: 1) only 15.6% of patients undergoing RRH which was a relatively small sample; 2) data on tumor size, postoperative histopathology, and adjuvant treatment were severely missing; 3) the survival rate in the ARH group was too high, with its 3-year OS of 99. 0%, compared with a 5-year OS of 94% in ARH in a large retrospective study of FIGO stage IB1 patients by Park *et al.* [19]; 4) only two patients per center per year, whose surgical experience and quality of the surgery by surgeons in MIS group had to be questioned; and 5) the grossly uneven distribution of recurrent cases, with all recurrent cases concentrated in 14 of the 33 centers.

MIS had been shown safe and feasible in endometrial [20] and rectal cancers [21]. In this regard, some possible reasons have been suggested to explain the disadvantages of cervical cancer: firstly, contact compression of the tumor tissue in the cervical region by the uterine manipulator, the vaginal incision under direct vision, may lead to spillage of tumor cells into the pelvis, resulting in local recurrence. Kanao *et al.* used a "no-look no-touch" technique and concluded that survival outcomes were similar in the MIS and open groups [22]. In addition, the size of the tumor diameter should be considered. Recent studies have shown that tumors <2 cm are more suitable for MIS [23]. Ponce *et al.* retrospectively collected data from 9 consecutive years of RRH in Spanish and Portuguese centers and demonstrated that tumors >2 cm was an independent risk

factor for recurrence (HR: 2.37) [24].

In summary, new technology is always evolving and MIS should not be completely dismissed. By improving the surgical experience of the gynecologist, rational patient selection, and strict tumor-free principles, MIS can bring benefits to ECC.

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