Critical Reviews in Oncology / Hematology 143 (2019) 76–80

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Advances in laparoscopic surgery for cervical cancer

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ARTICLE INFO

Keywords:
Laparoscopy
Robotic-assisted
Radical hysterectomy
Cervical cancer

ABSTRACT

In the recent years, minimally invasive surgery has emerged as the gold standard for the treatment of both benign and malignant gynecological conditions. Growing evidence suggest that laparoscopic and robotic-assisted treatments allow to archived the same long-term outcomes than conventional open abdominal treatments, minimizing peri-operative morbidity. In the present review we analyzed the advances in the treatment of cervical cancer patients, reporting the advances in both the evolution of concept of radical hysterectomy and of the adoption of minimally invasive surgery. We discussed the advantages related to the introduction of minimally invasive treatment for cervical cancer patients; innovation of conventional laparoscopic surgery as discussed as well. Recent evidence suggested a potential detrimental effect on long-term survival outcomes related to the use of minimally invasive surgery in patients affected by cervical cancer. However, reasons why minimally invasive surgery might have a detrimental effect are still unclear. Further evidence is needed in order to improve quality of treatment for cervical cancer patients.

1. Introduction

In spite of the large implementation of screening programs in developed countries, cervical cancer still is a major health issue, accounting for more than 12,800 and 4200 new diagnoses and deaths for the year 2017, in the US (Siegel et al., 2017). Additionally, cervical cancer represents the second most common cause of cancer-related death among women aged between 20 and 39 years (Siegel et al., 2013).

During the last two decades, the role of minimally invasive surgery has emerged, dramatically (Spirtos et al., 2002a; Nam et al., 2012; Querleu, 1993). Accumulating evidence suggested that laparoscopic and robotic assisted surgery guarantee better outcomes than traditional open abdominal procedures, in the setting of both benign and malignant disease (Obermair et al., 2008; Raspagliesi et al., 2017; Rendon et al., 2016; JandaM et al., 2015). Several prospective studies and few randomized trials underlined that minimally-invasive surgery improves short-term outcomes of apparent early stage endometrial cancer patients. The long-term of the LAP2 trial demonstrated that minimally invasive surgery improves short-term peri-operative outcomes without compromising long-term oncologic results (JandaM et al., 2015; Walker et al., 2012, 2009).

However, to date no randomized trial evaluated the efficacy of minimally invasive surgery in cervical cancer patients. Several retrospective and prospective studies investigated the role of minimally invasive surgery in cervical cancer patients, reporting that minimally invasive approach guarantees a reduction of postoperative morbidity in this cluster of patients (Conrad et al., 2015; Tanaka et al., 2017; Di Martino et al., 2017; Soliman et al., 2011; Salvo et al., 2017; Fagotti et al., 2014; Geisler et al., 2010; Hoogendam et al., 2014; Chiantera et al., 2015; Sert et al., 2016). Interestingly, despite the lack of a LAP2-equivalent study in radical hysterectomy (RH), 81% of the Society for Gynecologic Oncology members surveyed agreed that minimally invasive surgery (MIS) has a role in the management of early-stage cervical cancer (Conrad et al., 2015).

Notwithstanding, the utilization of minimally invasive techniques for the treatment of cancer of the uterine cervix has evolved slower than expected. The need of achieving surgical radicality and the execution of challenging procedures as radical hysterectomy has impacted on the prevalence of minimally invasive procedure rates (Conrad et al., 2015). In fact, although accumulating data suggested that minimally invasive radical hysterectomy guarantees the same oncologic outcomes of open procedures with improved surgery-related outcomes, minimally invasive procedure is not yet considered the standard of care. In the present review we highlight the role of minimally invasive radical hysterectomy focusing on surgical techniques, complication rates and

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https://doi.org/10.1016/j.critrevonc.2019.07.021
Received 7 May 2018; Received in revised form 2 August 2018; Accepted 29 July 2019

oncologic outcomes.

2. Development of the minimally invasive radical hysterectomy

Since 1987, Daniel Dargent firstly performed a minimally invasive radical hysterectomy combining the radical vaginal hysterectomy with a laparoscopic pelvic lymphadenectomy (Zakashansky et al., 2009). Following this pioneeristic report, Nezhat published the case report of the first laparoscopic radical hysterectomies with lymph node dissection (Nezhat et al., 1992). This preliminary experience was subsequently confirmed by other Authors who demonstrated the feasibility and safety of the laparoscopic techniques for the execution of radical hysterectomy (Sedlacek et al., 1994; Ting, 1994). In 1998, Jennings et al. published a retrospective study investigating the impact of integration of operative laparoscopy on length of stay and complication rates on an academic gynecologic oncology service. This study showed that the aggressive utilization of operative laparoscopy into the surgical practice of a gynecologic oncology service demonstrates significant improvements in length of stay without adversely affecting surgical complication rates (Jennings et al., 1998). In 2002, Spirtos et al. published a prospective study aiming to determine the risk of recurrence and to quantify morbidity and mortality rates in patients with cervical cancer who consented to undergo laparoscopic radical hysterectomy and retroperitoneal lymphadenectomy. This was the first large series on this issue including 78 consecutive patients with stage IA(2) and IB cervical cancer with at least 3 years of follow-up. This study demonstrated that laparoscopic radical hysterectomy could be successfully completed in patients with early-stage cervical cancer with acceptable morbidity. Intermediate-term follow-up validates the adequacy of this procedure (Spirtos et al., 2002b). In 2006, Sert et al., published the first case of robotic-assisted class III radical hysterectomy (Sert and Abeler, 2006). In 2012, the Society of Gynecologic Oncology released a consensus statement citing the non-inferiority of robotic-assisted surgery when compared to standard laparoscopic surgery (Spirtos et al., 2002b; Sert and Abeler, 2006).

3. Surgical technique of radical hysterectomy

Radical hysterectomy refers to the excision of the uterus en bloc with the parametria (ie, round, broad, cardinal, and uterosacral ligaments) and the upper one-third of the vagina. The most used way to classify radical hysterectomy was according to the Piver–Rutledge–Smith classification that was published in 1974 (Piver et al., 1974). This classification distinguishes five classes of radical hysterectomy, but has several major limitations. The original description of the five classes does not refer to clear anatomical landmarks or international anatomical definitions. The vaginal extent of resection is systematically referred to pericervical extent; vaginal resection is exaggerated from a third to three-quarters of the vagina. Furthermore, it includes a class I category, which is not radical hysterectomy, and a class V category, which is no longer used in current clinical practice. In addition, the rationale and anatomy for differentiation between class III and IV are unclear. Finally, The classification by Piver and colleagues does not take in consideration the concept of nerve preservation that was introduced in the 1950s (Kobayashi, 1961), subsequently refined by Japanese surgeons and adopted by European surgeons (Yabuki et al., 1996; Sakuragi et al., 2005a; Fujii et al., 2007; Trimbos et al., 2001).

In 2008, Querleu and Morrow proposed a new classification system based on surgical radicality (Querleu and Morrow, 2008). Radical hysterectomy is classified in type A (corresponding to the common extrafascial hysterectomy), type B (corresponding to the modified radical hysterectomy) where identification of autonomic nerves is not required, and the hypogastric plexus remains fully preserved), type C (including type C1 procedure, which corresponds to the nerve-sparing radical hysterectomy, and the type C2, which aims for a complete parametrial resection) and type D (requiring resection of the internal iliac vessels, together with their branches, including the gluteal, obturator and internal pudendal vessels). A part the execution of classical type A hysterectomy and type D radical hysterectomy that is reserved only in particular conditions (e.g., huge cervical tumors not responsive to other treatment modalities), patients affected by cervical cancer are likely to underwent to type B and type C radical hysterectomy, according to patients' and disease characteristics. Laparoscopic or robotic-assisted nerve sparing radical hysterectomy is technically similar to conventional nerve sparing radical hysterectomy with some specific minimally invasive steps. The isolation of hypogastric nerves and splanchnic nerves are performed as well as open surgery with the great advantage given by fine manipulation and magnified visual field. Recognition of bladder branches of pelvic nerves on the posterior layer of the vesico-uterine ligament is the critical issue for laparoscopic nerve-sparing radical hysterectomy. Sakuragi et al., described the identification, isolation, and preservation of these branches in open surgery (Sakuragi et al., 2005b). Nerve-sparing approach represents the way to reduce pelvic for dysfunctions in patients undergoing radical extirpation of the uterus. Accumulating evidence supports that nerve-sparing radical hysterectomy reduced voiding dysfunctions as well as rectal and sexual issues in comparison to conventional radical hysterectomy (Covens et al., 2001; Zullo et al., 2003).

4. Minimally invasive surgical treatment of early stage and locally-advanced cervical cancer

According with the data of other gynecological malignancies, data on the utilization of minimally invasive surgery in cervical cancer are related to patients affected by early stage disease. A growing number of investigations focused on the role of minimally invasive radical hysterectomy (type B or type C1) in patients with cervical confined disease (Obermair et al., 2008; Raspagliesi et al., 2017). Recently, few reports investigated the role of minimally invasive surgery in patients having locally-advanced cervical cancer. Although standard treatment for locally advanced stage cervical cancer includes chemo-radiation, a few patients (especially in European and Asian countries) have surgical treatment after the execution of neoadjuvant chemotherapy.

Recently, Gupta et al., reported data from a randomized controlled trial comparing the execution of neadjuvant chemotherapy plus radical surgery vs. radio plus chemotherapy in locally advanced cervical cancer (Gupta et al., 2018). The authors observed that the execution of concomitant chemoradiation resulted in superior disease-free survival compared with neoadjuvant chemotherapy followed by radical surgery in locally advanced cervical cancer. No differences in term of overall survival were observed. However, patients having neoadjuvant chemotherapy plus surgery experieced a lower risk of developing delayed toxicitis in comparison to concomitant chemoradiation (rectal: 2.2% v 3.5%,; bladder: 1.6% v 3.5%,; and vaginal: 12.0% v 25.6%) (Gupta et al., 2018). Although further evidence is needed a selected group of young patients might have a benefit from the use of neoadjuvant chemotherapy instead of concomitant chemoradiation.

A recent multi-institutional Italian study (involving also our center) collected data of women affected by locally advanced stage cervical cancer undergoing type C1 and type C2 radical hysterectomy. This paper highlights that both techniques are safe and effective. The data suggested that nerve-sparing approach is associated with improved outcomes in comparison to type C2 radical hysterectomy (Raspagliesi et al., 2017). In particular, this study underlined that 60-day pelvic floor dysfunction rates (including voiding, fecal and sexual alterations) were lower for patients having nerve-sparing radical hysterectomy in comparison to control group (Raspagliesi et al., 2017).

5. Complication and pelvic floor dysfunction rates following radical hysterectomy

Radical hysterectomy for cervical cancer is associated with an

intraoperative complication rate ranging from 1% to 6% even when performed via minimally invasive surgery (Sert and Abeler, 2006; Piver et al., 1974). Postoperative complications occurring within the first 30 days after surgery are the more significant source of morbidity. Minimally invasive surgery seems to be preferable over open abdominal procedures in terms of surgery-related morbidity in patients requiring radical hysterectomy (Boggess et al., 2008). This is in agreement with the conclusion of a recent meta-analysis by Shazly et al, underlined that minimally invasive radical hysterectomy may be superior to open abdominal radical hysterectomy with lower estimated blood loss, shorter hospital stay, less febrile morbidity, and wound-related complications (Shazly et al., 2015).

Urinary dysfunction/deficit such as loss of sensation or loss of motor function are noted in 70–80% of patients undergoing conventional radical hysterectomy (Serati et al., 2009). Later complications of radical hysterectomy, which arise beyond a 30-day time span, include sexual and rectal dysfunction and significant lymphoedema as well as symptomatic lymphoceles (in patients having pelvic node dissection) (Serati et al., 2009; Xiao et al., 2016; Bogani et al., 2014a, b).

Although the occurrence of pelvic floor dysfunction impacted significantly on quality of life, postoperative quality of life and sexual activity in patients have not been well compared between minimally invasive radical hysterectomy and open abdominal radical hysterectomy. There are no gold standard or objective indicators in the diagnosis of female sexual dysfunction, and the diagnosis mainly relies on clinical judgment. Since radical hysterectomy itself could significantly impair female sexual function regardless of the surgical approach, there appeared to be no significant differences in the female sexual function index between laparoscopic and open abdominal radical hysterectomy (Serati et al., 2009; Xiao et al., 2016). According to the data of the Literature, patients undergoing radical hysterectomy experience a significant decreased in arousability in about 25% of cases (Serati et al., 2009; Xiao et al., 2016; Bogani et al., 2014a). It is of interest that laparoscopic nerve-sparing radical hysterectomy impairs postoperative sexual function less than laparoscopic radical hysterectomy (Bogani et al., 2014a), probably to the magnificent view during laparoscopic dissection of the nerves.

Although minimally invasive and nerve-sparing techniques reduced the incidence of these complications by some accounts, they are still more prevalent than when compared to simple hysterectomy (Persson et al., 2009; Bogani et al., 2014c; Wang et al., 2015). Hypogastric plexus and nerves contain sympathetic fibers that fuse with nerves from the inferior hypogastric plexus. This complex system is responsible for sexual arousal, detrusor contractility, vaginal lubrication, and proper functioning of the rectal sphincter. These nerves are situated near the dorsal portion of the parametrial tissue, which is excised during radical extirpation of the uterus. Patient outcomes could exponentially improve if avoiding radical surgery where possible can spare these areas.

6. Evolution of laparoscopic radical hysterectomy

Constant attempts are done in order to improve safety, feasibility and effectiveness of conventional laparoscopic surgery. In fact, laparoscopic surgery continues to evolve: robotic-assisted surgery, single site and mini-laparoscopy represent the most utilized evolution of conventional laparoscopic surgery.

Robotic-assisted surgery has emerged in the recent years as an evolution of standard laparoscopy. Thanks to the robotic assistance, the minimally invasive instruments might be manipulated with extremely fine and precise movements. Moreover, the use of a computer enhanced, stereoscopic camera to give the surgeon the clearest possible three-dimensional visualization of the surgical field (Shazly et al., 2015). A recently published meta-analysis collecting data of 26 non-randomized studies, suggested that robotic radical hysterectomy is superior to open abdominal procedure in terms of short-term outcomes (length of hospital stay, febrile morbidity and wound complications) (Shazly et al., 2015). While, short-term outcomes are similar comparing robotic-assisted and laparoscopic procedures (Shazly et al., 2015).

Other authors reported very encouraging outcomes for patients treated with robotic-assisted surgery (Di Martino et al., 2017; Soliman et al., 2011; Wang et al., 2015). Similarly, although data regarding mini-laparoscopy and single site radical hysterectomy are scant, they seem to be related to improved outcomes in comparison to conventional laparoscopic procedures, especially in term of cosmesis and post-operative pain (Fagotti et al., 2014). Fagotti et al., performed a study comparing single-site and mini-laparoscopic radical hysterectomy. They observed that single site operation correlated with longer operative time but resulted in shorter length of hospital stay in comparison to mini-laparoscopy (Fagotti et al., 2014). However, owing to the low level of evidence on this issue further trials are needed to better understand the potential advantages of these new techniques over conventional laparoscopy.

7. Sentinel node mapping in cervical cancer

Accumulating data underlined the feasibility and safety of sentinel node mapping (the excision of the first lymph node / groups of nodes that cancer cells drain) in cervical cancer. The growing adoption of minimally invasive surgery contributed to the increased popularity in sentinel node mapping (Tanaka et al., 2017; Di Martino et al., 2017; Salvo et al., 2017). The adoption of innovative laparoscopic and robotic-assisted systems including softwares for the identification of sentinel nodes represents one of the major advantages for patients. Salvo et al., reported intriguing results related to the adoption of sentinel node mapping in cervical cancer (Salvo et al., 2017). Evaluating 188 patients with early stage cervical cancer undergoing sentinel node mapping followed by complete pelvic node dissection, they observed that only one patient had flase negative result (Salvo et al., 2017). According to their data, sensitività of sentinel node mapping was 96.4% (95% CI 79.8%–99.8%) and negative predictive value was 99.3% (95% CI 95.6%–100%). The false-negative rate was 3.6% (Salvo et al., 2017). Interestingly, tumor size and prior conization have not impact in the accuracy of sentinel node mapping. Other authors observed encouraging results on the adoption of sentinel node mapping during minimally invasive surgery for cervical cancer (Tanaka et al., 2017; Di Martino et al., 2017). Further randomized study are warranted in order assess the real advantages of the sole sentinel mapping in cervical cancer patients.

8. Oncologic outcomes

In the last decade, an increasing number of reports of patients having minimally invasive radical hysterectomy have been published (Nam et al., 2012; Soliman et al., 2011; Salvo et al., 2017; Fagotti et al., 2014; Geisler et al., 2010; Hoogendam et al., 2014; Chiantera et al., 2015; Sert et al., 2016). The results of these studies suggested that patients having minimally invasive surgery experienced the same long-term outcomes of patients having conventional open surgery (Nam et al., 2012; Soliman et al., 2011; Salvo et al., 2017; Fagotti et al., 2014; Geisler et al., 2010; Hoogendam et al., 2014; Chiantera et al., 2015; Sert et al., 2016). However, recent data underline that the utilization of minimally invasive surgery might negatively impact long-term outcomes of patients affected by cervical cancer (Ramirez et al., 2018; Rauh-Hain, 2018). The data from the Laparoscopic Approach to Carcinoma of the Cervix (LACC) study presented by Ramirex PT at the Society of Gynecologic Oncology (SGO) Annual Meeting in 2018 underlined a potential detrimental effect related to the adoption of minimally invasive surgery (Ramirez et al., 2018). The LACC study is a phase III randomized controlled study comparing minimally invasive (i.e., laparoscopic or robotic-assisted) vs. open abdominal radical hysterectomy and enrolling more than 600 patients affected by early stage cervical cancer in 33 centers around the world. Minimally invasive

radical hysterectomy was associated with higher rates of locoregional recurrence than open abdominal operations. The number of disease recurrences after laparoscopic or robotic-assisted procedures was almost four times (27 vs. 7) higher than the number of recurrences after open surgery (Ramirez et al., 2018). Data of more than 2200 cervical cancer patients included in the Surveillance, Epidemiology & End Result (SEER) database reported similar results (Rauh-Hain, 2018). The analysis of SEER database reporetd that 4-year mortality risks were 5.8% and 8.4% for open and minially invasive surgery, respectively (HR1.48 (95% CI 1.10–1.98)). The use of intrauterine manipulator, type of intra-abdominal colpotomy and the flow of gas into the abdominal cavity as well as the non-standardized learning curves among surgeons might be the reason of these unexpected results. However, further evidence is needed before abandoning minimally invasive technique in this setting.

9. Conclusions

The present review highlighted the current evidence regarding the role of minimally invasive surgery for the management of cervical cancer patients. We observed that in the recent years several retrospective and prospective studies underlined the safety, efficacy and effectiveness of minimally invasive radical hysterectomy. In according to the data available in the Literature, minimally invasive radical hysterectomy is associated with better perioperative outcomes in comparison to open surgery. Generally minimally invasive approach correlated with lower blood loss and shorter hospital stay, while it increase operative time in comparison to standard open abdominal procedures. Although recent data underline that minimally invasive radical hysterectomy might correlate with worse survival outcomes than conventional open surgery, further evidence is needed in order to weight pro and cons (in terms of surgical-related outcomes, survival and costs) of the adoption of minimally invasive surgery in patients affected by cervical cancer.

Declaration of Competing Interest

No funding sources supported this investigation

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