Executive Summary

Clinical Safety and Effectiveness of Robotic Surgery (2)

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▢ Background

Colon cancer is a malignant tumor that occurs in the colon and accounts for 7.18% of the overall cancer incidence rate in Korea. Open surgery is the most traditional procedure used for colon cancer, but with the introduction of laparoscopic surgery in the early 1990s and robotic surgery in the early 2000s, all three surgical methods are currently being used in Korea.

Esophageal cancer is a cancer of the esophagus with a very low overall cancer incidence rate of 0.9% in Korea. Surgery for esophageal cancer in Korea mainly consists of open surgery or video assisted thoracoscopic surgery (VATS), and robotic surgery is currently at the introductory stage.

Bladder cancer is a malignant tumor of the bladder that represents 1.6% of overall cancer incidence rate in Korea and shows the second highest incidence among urological cancers. Open surgery is the standard method used for bladder cancer. However, due to the drawback of its high

invasiveness, minimally invasive surgery has been studied, while minimally invasive surgery utilizing robotic surgery has recently been attempted.

Adrenal cancer is a malignant tumor of the adrenal cortex that is extremely rare with an overall incidence rate of 0.1% in Korea. Robotic surgery for adrenal cancer is still at the introductory stage.

Pelvic cancer and ureter cancer are malignant tumors of the renal pelvis and ureter that account for 0.38% of the overall cancer prevalence in Korea. Laparoscopic surgery is the standard surgical method for renal pelvis and ureter cancer, while robotic surgery is still at the introductory stage.

Uterine cancer is largely divided into cervical cancer and endometrial cancer. Of the overall cancer incidence rate in Korea, endometrial cancer represents 0.9% and cervical cancer represents 1.7%. Open and laparoscopic surgeries are the standard surgical methods for these cancers and are widely performed currently, while robotic surgery is partially applied for early endometrial cancer and early cervical cancer.

Lung cancer is a malignant tumor of the lung that has the fourth highest cancer prevalence in Korea of about 10%. Lung cancer is classified into non-small cell carcinoma and small cell carcinoma according to clinical stage; surgical treatment is performed only for non-small cell carcinoma. A standard surgical method of lung cancer is VATS lobectomy, while robotic surgery is at the introductory stage.

Oral cancer, a head and neck cancer, is the generic term for cancers that occur in the oral cavity, and pharyngeal cancer and laryngeal cancer are those of the pharynx and larynx, respectively. Oral cancer, pharyngeal cancer, and laryngeal cancer manifest relatively low overall cancer incidence rate in Korea at 0.2%, 0.4%, and 0.5%, respectively. The laryngopharynx is an anatomically complex structure that plays an important role in speaking, eating, and breathing; as such, transoral robotic surgery (TORS), which has the advantages of improved visualization of the operating field and organ preservation, has been introduced. Lymph node metastasis occurs in an early stage of laryngopharynx cancer, and lymph node removal is also mostly performed at the same time with cancer lesion resection. Robot-assisted neck dissection (RAND) via the retroauricular approach has gained interest due to its favorable effects on

function and cosmesis in patients after surgery.

▢ Objective

This study aimed to investigate the clinical safety and effectiveness of robotic surgery in uterine cancer, colon cancer, esophageal cancer, bladder cancer, lung and bronchial cancer, oral and laryngopharynx cancer, and adrenal and renal pelvis and ureter cancer to provide scientific information helpful in the decision-making process of patients and public health workers.

▢ Methods

A systematic review was conducted to assess the safety and effectiveness outcomes of robotic surgery compared to conventional surgical methods for each cancer (colon, esophageal, bladder, adrenal, renal pelvis, ureter, uterine, lung and bronchial, and oral and laryngopharynx). Studies were searched using three international databases (Ovid-Medline, Ovid-EMBASE, Cochrane library) and five domestic databases (KoreaMed, KMbase, KISS, RISS, KisTi), and search strategies were established under agreement with clinical experts to ensure their adequacy. An assessment for risk of bias for the selected studies was performed utilizing the Cochrane RoB in experimental studies and RoBANS version 2 for observational studies. After extraction of the treatment effect size of the chosen studies after quality assessment, a meta-analysis was performed for each outcome of interest.

▢ Results

- In bladder cancer, robotic surgery showed low risks of major and overall complications compared to open surgery and also lower risks of sepsis, abscesses, and respiratory failure in individual complication analyses; however, the risk of stricture was higher in the robotic surgery group than the open surgery group.
- In endometrial cancer, robotic surgery manifested a lower risk of overall, intraoperative, and postoperative complications compared to open surgery and lowered the risks of wound, intestinal

obstruction/atresia, infection, fever, readmission, ICU stay, and transfusion complications in individual complication analyses but a higher risk of vaginal cuff dehiscence. In surgery-related outcome analyses, robotic surgery reduced hospital stay and blood loss but prolonged operative time compared to open surgery. Compared with the laparoscopic surgery group, the robotic surgery group exhibited a lower risk of conversion to open surgery as well as overall, intraoperative, and postoperative complications and a lower risk of urinary damage and cystotomy among individual complications.

- In cervical cancer, robotic surgery had a lower risk of wound infection, urinary tract infection, fever, and transfusion but a higher risk of vaginal cuff complications than open surgery. In surgery-related outcome analyses, robotic surgery shortened the hospital stay and blood loss but delayed operative time. Compared with laparoscopic surgery group, only transfusion and complication risks were significantly lower in the robotic surgery group.

Ⅰ. Colon cancer

1. Robotic VS. Open surgery

One study of 135 subjects with colon cancer was included in our comparison of robotic surgery to open surgery. As a result of safety index analyses, 30-day mortality and overall complications after surgery did not differ significantly. Effectiveness index analyses revealed that readmission rate, the need for transfusion, and the number of retrieved lymph nodes did not differ significantly, whereas robotic surgery significantly increased operative time (median 191.7 vs 136.2, <.0001), shortened the hospital stay (median 5.0 vs 8.0, <.0001), and decreased the blood loss (median 6.1 vs 94.8, <.0001).

2. Robotic VS. Laparoscopic surgery

A total of five studies with 640 subjects with colon cancer were included in our comparison of robotic surgery to laparoscopic surgery. No significant

difference was shown in any of the indices between the robotic and laparoscopic surgery groups on safety index analysis. On the effectiveness index analysis, the robotic surgery group had a reduced time to regular diet (MD -0.69 days, 95% CI -1.11, -0.26, I^2=0%), time to flatus (MD -0.53 days, 95% CI -0.76, -0.30, I^2=48%), time to bowel function recovery (MD -0.62 days, 95% CI -0.77, -0.47, I^2=69%), hospital stay (MD -0.64 days, 95% CI -1.10, -0.18, I^2=48%), and blood loss (MD -19.49ml, 95% CI -27.10, -11.89, I^2=0%) and an increased distal resection margin (MD 2.59cm, 95% CI 1.40, 3.77, I^2=0%) compared to the open surgery group but a prolonged operation time (MD 51.98 mins, 95%CI 39.59, 64.37, I^2=10%).

Ⅱ.Esophageal cancer

1. Robotic VS. Thoracoscopic surgery

One study with 37 subjects with esophageal cancer was included in the comparison of robotic and thoracoscopic surgery. No statistically significant difference was shown in safety and effectiveness outcomes.

2. Robotic surgery

Nine studies with a total of 235 subjects with esophageal cancer were included in our analysis of robotic surgery. On the safety indices, integrated estimates indicated 30-daymortality (5.3%, 95%CI 2.4, 11.3), conversion to open surgery (15.3%, 95% CI 9.0, 24.7), pneumonia (10.9%, 95%CI 6.0, 19.2), vocal cord paralysis (24.2%, 95% CI 16.6, 34.0), atrial fibrillation (11.5%, 95% CI 7.0, 18.1), anastomotic leak (18.9%, 95% CI 13.7, 25.4), empyema (7.6%, 95% CI 3.2, 16.9), chylothorax (9.2%, 95% CI 4.8, 16.7), and wound infection (7.5%, 95% CI 3.4, 15.7). On the effectiveness indices, the number of retrieved lymph nodes, operative time, blood loss, hospital stay, ICU stay, and number of patients requiring respirator use were reported. Differences were seen among the studies.

Ⅲ. Bladder cancer

1. Robotic VS. Open surgery

A total of 19 studies with 2,446 patients with bladder cancer were included in the comparison of robotic surgery to open surgery. The safety index analyses showed that the 90-day major and overall complication incidences (RR 0.57, 95% CI 0.42, 0.76; RR 0.73, 95% CI 0.65, 0.82) were significantly lower in the robotic surgery group than in the open surgery group. Inindividual complications, the robotic surgery group showed significantly lower incidences of sepsis (RR 0.25, 95% CI 0.11, 0.58), abscess (RR 0.49, 95% CI 0.24, 0.99), and respiratory failure (RR 0.19, 95% CI 0.04, 0.78) than the open surgery group, whereas the open surgery group manifested a lower stricture incidence (RR 1.99, 95% CI 1.21, 3.28) than the robotic surgery group. The effectiveness index analyses revealed that the robotic surgery group had less blood loss (MD 505, 95% CI -0.39, 7.08, I^2=60%) and a lower transfusion rate (RR 0.32, 95% CI 0.20, 0.52, I^2=79%) than the open surgery group. In addition, the robotic surgery group had a decreased time to flatus, decreased time to regular diet, and shorter hospital stay at 0.6 (95%CI -0.83, -0.46, I^2=94%), 1.3 (95% CI -2.05, -0.57, I^2=62%), and 1.2 (95% CI -2.18, -0.31) days, respectively, compared to the open surgery group. The operative time was approximately 102 minutes (95% CI 80.35, 124.85) longer in the robotic surgery group than the open surgery group.

2. Robotic VS. Laparoscopic surgery

A total of three studies with 279 subjects with bladder cancer were included in the comparison of robotic and laparoscopic surgery. The safety index analyses revealed no significant difference between groups. The effectiveness index analyses showed that the robotic surgery group had reduced blood loss (MD 293, 95% CI -589.54, -7.33, I^2=96%) and hospital stay (MD 5.23, 95% CI -7.23, -3.22) compared to the open surgery group.

Ⅳ. Adrenal cancer

There was no study comparing robotic surgery and existing surgery in adrenal cancer.

V. Renal pelvis and ureter cancer

1. Robotic VS. Laparoscopic surgery

Only one study with a total of 44 patients reported the use of robotic and laparoscopic surgery for renal pelvis and ureter cancer. This study showed that robotic surgery was as safe as laparoscopic surgery.

2. Robotic VS. Laparoscopic and open surgery

One study with 20 patients compared robotic, laparoscopic, and open surgery for renal pelvis and ureter cancer. Although it did not directly compare robotic and conventional surgery, robotic surgery reduced blood loss and hospital stay.

VI. Uterine cancer

1. Robotic VS. Open surgery

In endometrial cancer, a total of 19 studies with 3,062 subjects were included in the comparison of robotic surgery to open surgery. Robotic surgery had a significantly lower incidence of overall complications (RR 0.37, 95% CI 0.28, 0.49), intraoperative complications (RR 0.40, 95% CI 0.23, 0.72), and postoperative complications (RR 0.49, 95% CI 0.36, 0.68) compared to open surgery. Among the individual complications, robotic surgery also showed a lower incidence of wound infection (RR 0.12, 95% CI 0.05, 0.33), wound dehiscence (RR 0.11, 95% CI 0.03, 0.37), wound complications (RR 0.83, 95% CI 0.19, 3.66), ileus/bowel obstruction (RR 0.18, 95% CI 0.10, 0.32), infection (RR 0.29, 95% CI 0.16, 0.54), fever (RR 0.21, 95% CI 0.06, 0.75), readmission (RR 0.44, 95% CI 0.26, 0.73), ICU stay (RR 0.16, 95% CI 0.05, 0.56), and transfusion (RR 0.28, 95% CI 0.19, 0.40) but a higher risk of vaginal cuff dehiscence/separation (RR 3.03, 95% CI 1.35, 6.80). In peri-operative outcomes, hospital stay (MD -2.85, 95% CI -3.28, -2.41, I^2=91%) and blood loss (MD -159.62, 95% CI -189.73, -129.50, I^2=83%)

were significantly decreased in robotic surgery, whereas operation time (MD 44.15, 95% CI 20.91, 67.39, I^2=98%) was increased, while the oncologic outcomes such as survival rate or recurrence did not show a significant difference between the two groups. In patient report outcomes, Hoekstra et al (2009) reported that a significantly less pain medications was used in the robotic surgery group, while time to return to daily life (Bell et al, 2008) was also significantly shorter in the robotic surgery group.

In cervical cancer, a total of 14 studies with 994 subjects were included in the comparison of robotic surgery to open surgery. In safety outcomes, the incidence of overall complications, intraoperative complications, and postoperative complications showed no significant difference. Vaginal cuff complications (RR 3.16, 95% CI 1.00, 9.99) showed a marginally significantly higher incidence in robotic surgery compared to open surgery; among individual complications, the incidences of urinary tract infection (RR 0.27, 95% CI 0.09, 0.82), wound infection (RR 0.24, 95% CI 0.06, 0.89), fever (RR 0.28, 95% CI 0.12, 0.69), and transfusion (RR 0.12, 95% CI 0.06, 0.24) were lower in the robotic surgery than in the open surgery group. In peri-operative outcomes, robotic surgery showed shorter hospital stay (MD -3.95, 95% CI -5.78, -2.12, I^2=96%) and less blood loss (MD -326.72, 95% CI -440.31, -213.12, I^2=90%) than open surgery but longer operation time (MD 27.94, 95% CI 0.48, 55.39, I^2=95%) and significantly lower number of retrieved pelvic lymph nodes (MD 3.71, 95% CI −5.88, -1.53, I^2=52%). Overall survival and disease free survival were reported no significant difference in three studies, whereas mortality and recurrence rates differed significantly in some studies. However, it was reported that the outcome should be carefully interpreted because of differences in underlying conditions and follow-up duration between the two groups. Patient-reported outcomes included per one study showed a lower pain score (mean 2.5 vs 3.5), lesser amount of opioids use (82% vs 100%), shorter duration of analgesic use (MD -18.7, 95% CI −22.59, -14.81), and significantly shorter time to a return to work in the robotic compared to the open surgery group.

2. Robotic VS. Laparoscopic surgery

In endometrial cancer, a total of 22 studies with 3,512 subjects were included in the analysis of robotic versus laparoscopic surgery. No studies reported a significant difference in oncological outcomes (survival rate, recurrence) between the robotic and laparoscopic surgery groups. The incidence of conversion to open surgery showed a significantly lower in the robotic surgery group (RR 0.35, 95% CI 0.23, 0.52), overall complications (RR 0.73, 95% CI 0.54, 0.98), intraoperative complications (RR 0.24, 95% CI 0.12, 0.48), and postoperative complications (RR 0.73, 95% CI 0.54-0.98) in the robotic group compared to the laparoscopic group; of the individual complications, the incidence of urinary damage (RR 0.20, 95% CI 0.04, 0.91) and cystotomy (RR 0.21, 95% CI 0.06, 0.74) was lower as well. In perioperative outcomes, robotic surgery shortened the hospital stay (MD -0.50, 95% CI -0.94, -0.07, I^2=88%) compared to laparoscopic surgery and had a reduced blood loss (MD 94, 95% CI -105.46, -82.86, I^2=51%). One study (Leitaoet al., 2013) reported that significantly smaller amounts of fentanyl were used in the robotic group.

In cervical cancer, a total of eight studies with 505 subjects were included in the comparison of robotic and laparoscopic surgery. Pooled analyses showed that robotic surgery group had a lower risk of transfusion (RR 0.24, 95% CI 0.06, 0.93) than in the laparoscopic surgery group, but there were no significant difference in other safety and effectiveness outcomes. One study (Soliman et al, 2013) reported that the amount of intravenous analgesic use was significantly lesser in the robotic group.

Ⅶ. Lung and bronchial cancer

1. Robotic VS. Open surgery

A total of two studies with 239 subjects were included in the comparison of robotic and open surgery for lung cancer. In the comparison between robotic and open surgery for lung cancer, there was no statistically significant difference in the safety and effectiveness indices.

2. Robotic VS. Thoracoscopic Surgery

Five studies with 405 subjects with lung cancer were included in the comparison of robotic and thoracoscopic surgery. In the comparison between robotic surgery and thoracoscopic surgery for lung cancer, there was no statistically significant difference in safety and effectiveness indices.

Ⅷ. Oral and laryngopharynngeal cancer

1. TORS VS. Open neck resection

A total of four studies with 199 subjects with primary laryngopharyngeal cancer were included in the comparison of TORS to open surgery. In primary laryngopharyngeal cancer, TORS showed a significantly lower free flap reconstruction rate (RR 0.15, 95% CI 0.03, 0.81) and tracheostomy rate at the time of surgery (RR 0.20, 95% CI 0.08, 0.05) compared to open surgery and had a significantly shorter time to oral diet of 10.2 days (MD -10.2, 95% CI -13.20, -7.00), time to decannulation of 6.4 days (MD -6.4 days, 95% CI -10.05, -2.81, I^2=78%), hospital stay of 8.5 days (MD -8.5, 95% CI -10.79, -6.11), and operative time of 135.9 minutes (MD -135.9, 95% CI -222.39, -49.41).

Two studies with 139 patients with recurrent laryngopharyngeal cancer were included in the comparison of TORS to open surgery. In recurrent laryngopharyngeal cancer, salvage surgery using robotic surgery manifested significantly lower 2-year disease-free survival rate (74% vs. 43%, p=0.01), 2-year overall survival rate (74% vs. 43%, p=0.02), positive margin rate (RR 0.32, 95% CI 0.14, 0.73), tracheostomy rate at the time of surgery (RR 0.33, 95% CI 0.22, 0.49), feeding-tube rate at the time of surgery (RR 0.48, 95% CI 0.34, 0.68), and feeding tube dependence rate at six-months after surgery (RR 0.27, 95% CI 0.14, 0.73) compared to open surgery.

2. TORS VS. Transoral Laser Microsurgery (TLM)

Two studies with 53 subjects with primary laryngopharyngeal cancer were included in the comparison of TORS to Transoral Laser Microsurgery (TLM). We found no statistically significant difference in the safety and

effectiveness indices of TORS versus TLM.

3. Robot-Assisted Neck Dissection (RAND) VS. Conventional transcervical neck dissection

A total of three studies were included in the comparison of RAND to conventional transcervical neck dissection in 109 patients with lymph node metastasis or suspected lymph node metastasis due to oral and laryngopharyngeal cancer. RAND showed significantly higher cosmetic satisfaction by 1.1 points (95% CI 0.24, 1.78, I^2=77%) than conventional transcervical neck dissection and a significantly longer operation time by 88 minutes (95% CI 64.90, 111.01, I^2=78%).

▢ Conclusions

In colon cancer, only one study reported a comparison of robotic and open surgery; therefore, it was not sufficient for the assessments. Comparison of laparoscopic and robotic surgery revealed more favorable outcomes in functional variables such as time to flatus and time to bowel movement, but sufficient evidence to make a clear conclusion is currently lacking. Therefore, a well-designed randomized clinical study with a long-term perspective is needed to assess robotic surgery treatment outcomes.

In esophageal cancer, one study compared the safety and effectiveness of robotic and conventional surgical methods used. Robotic surgery is currently rarely performed for esophageal cancer in Korea, but its use is expected to increase in cardiothoracic surgery once new robotic surgery devices are introduced in the future.

In bladder cancer, robotic surgery exhibited a lowered risk of major and individual complications including sepsis compared to open surgery. However, the result of a randomized clinical study was discrepant from that of a cohort study, thereby making it currently impossible to draw a confirmed conclusion. Considering that robotic surgery for bladder cancer is at an initial stage of implementation, a treatment outcome assessment through a prospective randomized clinical study after overcoming the learning curve is necessary.

In adrenal cancer, renal pelvis and ureter cancer there was a substantial lack of evidence in the assessment of safety and effectiveness between robotic and conventional surgical methods. Therefore, the accumulation of further evidence is required.

In cervical and endometrial cancer, robotic surgery was shown to lower the risk of wound complications, infection, and fever compared to open surgery but manifested a higher incidence of vaginal cuff complications. Oncological outcomes did not show a significant difference, and robotic surgery reduced the hospital stay and blood loss but prolonged the operative time. In the comparison with laparoscopic surgery for endometrial cancer, the robotic surgery group exhibited a lower risk of conversion to laparotomy as well as overall, intraoperative, and postoperative complications. Particularly in endometrial cancer, robotic surgery may be safer than conventional surgery. However, methodological quality and the level of evidence of the included studies are not high; therefore, we are unable to make a clear conclusion regarding the clinical effects of robotic surgery in uterine cancer. Further prospective studies or well-designed randomized clinical studies are required to validate these findings.

In lung and bronchial cancer, no indices showed a significant effect between robotic and conventional surgical methods, and it is necessary to accumulate evidence in this field to more clearly investigate safety and effectiveness.

In oral and laryngopharynngeal cancer, there was not enough evidence to draw a definite conclusion regarding safety and effectiveness between robotic surgery and conventional surgical methods. TORS is promising for oral and laryngopharyngeal cancer, but a well-designed prospective study is also required to clearly elucidate the clinical effects of robotic surgery.

Key words: Robotic surgery, Safety, Effectiveness, Colon cancer, Esophageal cancer, Baldder cancer, Adrenal cancer, Renal pelvis and ureter cancer, Cervical and endometrial cancer, Lung cancer, Oral and laryngopharynngeal cancer