Executive Summary

Clinical Effectiveness and Safety of Robotic Surgery

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□ Introduction

- In Korea, robot-assisted surgery uncovered by national health insurance has been often utilized in various areas such as urology, general surgery, obstetrics, gynecology, and thoracic surgery since it received Ministry of Food and Drug Safety (MFDS) approval in 2005.
- Compared with conventional open surgery, the benefits of robot-assisted surgery are as follows: low risk of infection, preventing excessive blood loss, minimized surgical related scars, and recovery faster for small incision.
- However, as there is large variation in surgical outcomes depending on the individual surgeon's rate of learning so that those who want to use the technology for their patients should overcome the learning curve. In addition, because of tactile limited, the side effects, such as perforations or organ injury, have been frequently reported.
- Experts in Korea have raised concerns about safety of the robot-assisted surgery procedures, pointing out that it is not cost-effective compared to existing technologies.
- This study is intended to evaluate safety and effectiveness of the robot-assisted surgery to five kinds of cancer disease (prostate cancer, kidney cancer, rectal cancer, gastric cancer, and thyroid cancer) which are the most frequently performed in Korea, through domestic

cohort data analysis and systematic literature review.

- The results of this study might be used as valuable resources in the clinical decision-making related to robot-assisted surgeries, and it is also expected to be used as primary information for establishing the relevant national health care policy.

□ Method

Ⅰ. Research for Current Status of robot-assisted surgeries in Korea

1. Current status

- In cooperation with Ministry of Health and Welfare and tertiary hospitals, we received whole hospital registries for 20,944 subjects through robot-assisted surgeries between September, 2005 and December, 2011 in Korea, and then linked up the data with national cause of deaths database of Statistics Korea, matching on identification numbers of the subjects. After that we linked up again the data set with the Health Insurance Review & Assessment Services's health insurance claims data between January 1, 2008, and December 31, 2012 and determined it as our final cohort data set for the study.
- Final subjects in the analysis using the cohort data only were chosen patients who received robotic surgical procedures for tumor in prostate, kidney, rectum, stomach, or thyroid in 2011.

2. Analysis

- We explored baseline characteristics of the subjects included the final data set, such as gender and age distribution, and then analyzed it by important indicators(mortality, hospital stay, ICU readmission, blood transfusion, anesthesia, etc.) based on consultation with clinical experts.

Ⅱ. Systematic Review of Literatures

1. Prostate cancer

- We performed a systematic review using existing systematic reviews (SR) to investigate clinical effectiveness and safety of robot-assisted surgery for prostate cancer, compared with open or laparoscopic surgery.
- R-AMSTAR was used to assess quality of the existing SRs and, as a result, two HTA reports published in 2011 and 2012, respectively, were selected as a available evidence with the best quality.
- RCT and comparative observational studies carried out on abroad and published from 2009

to August 2013 and domestic comparative studies were additionally included in the process. All meta-analyzes were performed on each of interested medical outcome, extracting the treatment effect size of both primary and secondary studies included.

2. Kidney cancer, rectal cancer, gastric cancer, thyroid cancer

- Full systematic review process was carried out on kidney cancer, rectal cancer, gastric cancer, and thyroid cancer, respectively.

- Database

· Ovid MEDLINE, Ovid Embase, and CENTRAL were primarily used to search related literatures. Domestic databases (Korea Med, KMbase, Kiss, Riss, KisTi) were also used to search studies conducted in domestic area.

- Inclusion / exclusion criteria

Inclusion criteria	Exclusion criteria
▪ Study that focused on patients with kidney, rectal, gastric, or thyroid cancer ▪ Study compared surgical and patients' outcomes between robot-assisted and existing technique(Open or Laparoscopic surgery)	▪ Study that did not focus on patients with kidney, rectal, gastric, or thyroid cancer ▪ Study that did not perform robot-assisted surgery ▪ Study that did not perform existing surgery procedure(open or Lapa) as a comparator ▪ Not primary studies (review article, letter, comment, systematic research review, meta-analysis research etc.) ▪ Gray literatures (Abstract only published or thesis, etc.) ▪ Preclinical study

- Quality assessment of the literatures included in the process

· MINORS and RoB of Cochrane was used in order to assess quality of observational studies and prospective randomized controlled studies, respectively.

- Data extraction
  · Method, target population, information relating to robotic and comparative technique, and important outcomes were extracted using a standardized data extraction form.
- Data analysis
  · Meta analysis was performed if the quantitative analysis is applicable, but if not, just brief descriptions were presented.

|||. Presentation meeting

- Objective
  · The meeting aimed to strengthen reliability and completeness of our study's results and spread our findings to related researchers and health care policy decision-makers, by sharing the study's results and hearing publically comments and suggestions from the participants.
  · When : December 18, 2013 (Thursday), 14:00 ~ 18:10
  · Where : National Evidence based Health care Collaborating Agency, Conference Room
  · Main Participants : 83 people, including 12 related academic associations, the relevant government departments in Ministry of Health and Welfare, Intuitive Surgical Korea, related researchers and clinicians.

□ Result

| . Prostate Cancer

1) Robot vs Open

- Robotic surgery when compared with open surgery is associated with low risk of complication (bladder neck contracture, organ injury, pulmonary embolism etc.) and low risk of peri-operative outcome. Also, robotic surgery is associated with reduction in the length of hospital stay, although there was high degree of heterogeneity. The risk of functional outcome was higher in robotic surgery compared open surgery. However, there was no significant difference between robotic and open surgery regarding oncological outcome.

2) Robot vs lapa

- The risk of complication, such as organ injury, major complication in Clavien Dindo classification) was lower in robotic surgery compared laparoscopic surgery. robotic surgery when compared with laparoscopic surgery is associated with improvement of functional

outcomes. Also, according to subgroup analysis robotic surgery has low risk of oncological outcomes.

II. Kidney Cancer

1) Robot vs open

- In partial nephrectomy, open surgery shows favorable tendency compared with robot-assisted surgery in the operative time and warm ischemia time (WIT), but the robot-assisted surgery shows a shorter hospital stay. However, the numbers of literature was limited and most of them were retrospective observational studies, indicating the quality of evidence was low.

2) Robot vs lapa

- In partial nephrectomy robot-assisted surgery shows 1) lower conversion rate to open surgery and radical nephrectomy, and 2) favourable estimated glomerular filtration rate (eGFR) that indicate the preservation of renal function. 3) reduction in the length of hospital stay, compared with laparoscopic surgery. But it is shown that the quality of evidence is low because most of included studies are retrospective observational studies.

III. Rectal Cancer

1) Robot vs open

- Robot-assisted surgery when compared with open surgery was associated with low risk of urinary retention.
- Both time to soft diet and flatus passage were significantly faster in the patients thorough robot-assisted surgery compared to open surgery, while operation time for robot-assisted surgery was longer than for open surgery.

2) Robot vs lapa

- Robot-assisted surgery when compared with laparoscopic surgery was associated with low risk of conversion rate to open surgery.
- Both time to soft diet and flatus passage were faster in the patients thorough robot-assisted surgery compared to laparoscopic surgery. However, there were no significant differences between those outcomes of both robot-assisted and laparoscopic surgery. And operation time for robot-assisted surgery was longer than those of laparoscopic surgery.

Ⅳ. Gastric Cancer

1) Robot vs Open

- The postoperative hospital stay in the RAG(Robot-Assisted Gastrectomy) group was shorter than in the OG(Open Gastrectomy) group. The estimated blood loss was more reduced in the RAG(Robot-Assisted Gastrectomy) group as compared with the OG(Open Gastrectomy) group. However, the operative time was longer in RAG(Robot-Assisted Gastrectomy) group than in the OG(Open Gastrectomy) group.

2) Robot vs Lapa

- The RAG(Robot-Assisted Gastrectomy) group showed shorter postoperative hospital stay, less estimated blood loss and starting time faster for soft diet, but the operative time in the RAG(Robot-Assisted Gastrectomy) group was longer than in the LAG(Laparoscopic-Assisted Gastrectomy) group.

Ⅴ. Thyroid Cancer

1) Robot vs open

- Regarding safety outcomes, robot-assisted thyroidectomy when compared with open thyroidectomy was associated with high risk of temporary vocal cord palsy. Volume of estimated blood loss, one of the outcomes evaluated effectiveness of the surgery, was smaller the robot-assisted thyroidectomy than the open thyroidectomy and also the robot-assisted group were more satisfied with post-operative cosmetic results at three months after the surgery, comparing with open surgery group.

2) Robot vs Endo

- Regarding safety outcomes, robot-assisted thyroidectomy when compared with endoscopic thyroidectomy was associated with high risk of temporary hypoparathyroidism. On the other hands, there were no significant differences between robot-assisted thyroidectomy and open thyroidectomy regarding effectiveness outcomes.

□ Strength and Limitation of the Study

1. Strength

- The findings of this study might be useful when establishing a health insurance policy related robot-assisted surgery.
- It would be a good resource to related clinicians and patients when they build treatment

strategy up .

2. Limitation

- In kidney, rectal, gastric, and thyroid cancer, the low quantity and poor quality of evidence were the major limitation on this study because of no prospective randomized controlled studies and lack of the absolute number of related literatures. Many studies in our review were reported insufficient follow-up period so that much of data from the studies was unsuitable for evaluation of oncological outcomes.

□ Conclusions and Policy Recommendations

1. Prostate Cancer

- Although there was high degree of heterogeneity, this study presented that robot surgery is superior in terms of safety, peri-operative outcome, functional outcome and oncological outcome compare the laparoscopic or open surgery. However it was not sufficient to support long term outcomes. Therefore, well designed long term follow-up prospective studies and cost effectiveness study are needed.

2. Kidney Cancer

- In order to evaluate the treatment effect of robotic surgery in partial nephrectomy, the numbers of literature were not sufficient, and the level of evidence is not high for evaluating treatment effects. Therefore, in order to evaluate the outcomes of robotic surgery, well designed randomized clinical study is required in the future.

3. Rectal Cancer

- The conversion rate to open surgery showed significantly low in robotic surgery. Recently, urinary function and sexual function after robotic surgery were more improved. Thus, it is expected that robotic surgery in rectal cancer patients is more increased. So this result needs to be verified by large prospective randomized clinical trials.

4. Gastric Cancer

- Comparing the surgical performance of the RAG(Robot-Assisted Gastrectomy) group and the LAG(Laparoscopic-Assisted Gastrectomy) group in gastric cancer, there was no difference in mortality rate and complication rate. The postoperative hospital stay in RAG(Robot-Assisted

Gastrectomy) group was slightly shorter than in the LAG(Laparoscopic-Assisted Gastrectomy) group.

- Considering the robotic surgery is the early stages in gastric cancer, the precise evaluation of surgical outcomes in clinical practice is necessary through the prospective randomized controlled study after overcoming the learning curve.

5. Thyroid Cancer

- Robot-assisted surgery for thyroid cancer is not minimally invasive technique but remote access technique so that it runs contrary to the view of robot-assisted surgery for other oncological disease, such as prostate cancer, which bring less pain or recovery faster up as the main strong points. In addition, it should be considered that new complications, brachial plexus injury, are reported even if it is rare.
- Considering very high cost for robotic thyroid surgery and lack of evidence on the surgical effectiveness, social consensus is essential to determine if the robot-assisted surgery is appropriate for patient with thyroid cancer.
- Well designed long term follow-up prospective studies are also needed to evaluate clinical safety and effectiveness based on sufficient quantity of evidence.

Key words: robotic surgery, safety, efficacy, prostate cancer, kidney cancer, rectal cancer, stomach cancer, thyroid cancer