Safety and efficiency of laparoscopic unassisted zero-ischemia enucleation for stage T1 renal carcinoma

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1. Research Background

Renal cell carcinoma(RCC) is a common tumor of the urinary system, accounting for 4.1% of all malignant tumors. 1 According to the latest GLOBOCAN data, in 2021, there are 71,676 new cases and 15,259 deaths of kidney cancer in the United States and 77,410 new cases and 46,345 deaths in China. The incidence of kidney cancer in China has increased at an average annual rate of 6.5% over the past 20 years and has surpassed bladder cancer in the number of deaths related to urological tumors, ranking first. Since renal ultrasound is a routine medical examination for people over 40 years old in China, most of the patients are in the early stage of limited renal cancer when they are diagnosed.

In the current guidelines, nephron sparing surgery(NSS) is the preferred treatment for early-stage limited kidney cancer. NSS includes partial nephrectomy(PN) and tumor enucleation(TE). Unlike PN, TE is a surgical procedure that bluntly separates the tumor along the natural cutting plane between the pseudocapsule and healthy parenchyma, completely removing the tumor tissue while maximizing the preservation of normal kidney tissue. However, most surgeons currently perform partial nephrectomy. The reason for this phenomenon is first, the problem of concept. most surgeons doubt whether TE can clean up tumor tissue. on the other hand, enucleation requires surgeons to have a better understanding of the anatomical relationship around the tumor and accurately separate the tumor envelope and normal kidney tissue, and its surgical difficulty is higher than that of traditional PN.

Our team has conducted a clinical meta-analysis on these two procedures, and the results showed that TE has the advantages of less trauma, faster postoperative recovery, and better protection of renal function than PN, without increasing the risk of tumor recurrence.

Minervini et al. analyzed the pseudocapsule integrity of 304 specimens after TE, founding that 51% of the specimens had an intact pseudocapsule and 49% had infiltrating tumor cells on the pseudocapsule. but all specimens had negative cut margins and there is no statistical difference in 5-year progression-free survival. thus they concluded that enucleation for renal cancer is a safe surgical procedure. In the past 10 years, our team has performed more than 500 kidney cancer enucleations without any positive margins and no patient has experienced in local recurrence. In addition, traditional PN requires temporary blockage of the renal artery to achieve a relatively bloodless operating environment to ensure the safety of tumor removal. But prolonged warm ischemia is bound to affect the function of normal kidney tissue. Therefore reducing thermal ischemia time up to zero ischemia time has become a quest for surgeons. The combination of zero-ischemia technique on the basis of kidney cancer enucleation is a field that has rarely been touched.

Therefore reducing thermal ischemia time up to zero ischemia time has become a quest for surgeons. Clinically, the combination of zero-ischemia technique on the basis of kidney cancer enucleation is a field that has rarely been touched. In the last 3 years, our team has performed nearly 100 cases of zero-ischemic renal tumor enucleation, and this procedure can maximize the protection of renal parenchyma and renal function under the premise of ensuring tumor safety. In conclusion, if zero ischemia enucleation can be applied and popularized to limited renal cancer surgery, it will benefit a large number of patients and improve the prognosis.

2. Research objectives

Main objective: the efficacy (rate of change in renal function GFR, overall survival OS, tumor-free survival TFS, progression-free survival PFS, etc.) and safety (positive incision margin rate, intraoperative blood loss, postoperative complication rate, etc.) of unassisted zero-ischemia enucleation in the surgical treatment of patients with early stage (T1) renal cancer.

Secondary objectives: differences between unassisted zero ischemic enucleation of renal cancer and partial nephrectomy with clamping of the hilum in the surgical management of patients with renal cancer and the role of the modified ABC score in the assessment of renal cancer.

3.Study content and design

This study aims to evaluate the effectiveness and safety of the surgery by using renal cancer patients who met the inclusion criteria. Summarizing the preoperative, perioperative, and postoperative data, and evaluating the operative time, intraoperative bleeding, postoperative hospitalization days, postoperative complication rate, postoperative short-term, intermediate, and long-term renal function indexes, overall survival, tumor-free survival, progression-free survival and postoperative renal cancer recurrence rate of the patients.

Statistical software is used to describe the characteristics of patient data. T-test, rank sum test, multi-factor regression, and cox regression are used to investigate the effects of each factor on the treatment outcome and prognosis of patients undergoing zero-ischemic renal enucleation, to describe whether there are differences in the safety and efficacy of zero ischemic renal enucleation compared with traditional

partial nephrectomy for the treatment of stage T1 renal carcinoma.

This study used a retrospective research trial design to include 73 patients who underwent zero-ischemic enucleation and 73 patients who underwent traditional partial nephrectomy from 2014 to 2022, for a total of 146 patients. The formula for calculating the sample size is as follows.

$$n = [z_\alpha \sqrt{2\bar{p}\bar{q}} + z_\beta \sqrt{p_0 q_0 + p_1 q_1}]^2 p / (p_1 - p_0)^2$$

Figure 1. Estimated sample size calculation

note：Zα、Zβ are the quartiles under standard normal distribution.
p1: Expected morbidity in the exposed group.
p0: Expected incidence in the control group.
q1: q1=1- p1.
q0: q0=1- p0.

4.Study population

4.1 Inclusion criteria

1. The age is between 18 and 80 years old.
2. Stage T1a or T1b according to the 8th edition of the AJCC TNM staging of kidney cancer, 2017.
3.The patients who underwent PN or TE between 2014 and 2022.

4.2 Exclusion criteria

1. With severe active infection or serious cardiac, hepatic, renal and hematopoietic diseases; and other physical conditions that make them unsuitable for the test in question (as judged by the investigator).
2. The patient has no measurable or evaluable lesions.
3. The tumor is close to the collecting system, touching the renal artery or renal vein, and other anatomical conditions that are not

suitable for nephrectomy.

4.History of organ transplantation or need for long-term adrenocorticotropic hormone therapy; hypothyroidism, adrenal or pituitary function that cannot be controlled with hormone replacement therapy alone, type I diabetes, psoriasis or vitiligo requiring systemic treatment, etc.

5. The presence of active infection requiring systemic therapy. The presence of human immunodeficiency virus (HIV) infection (known to be HIV antibody positive). The presence of active HBV or HCV infection (HBsAg positive individuals, or HBcAb positive but HBsAg negative individuals who require additional DNA quantification and whose results do not exceed the upper limit of normal values in the study center laboratory can participate in this study. Previous HCV infected patients with negative HCV RNA test results during the screening period can participate in this study).

6. Have a history of kidney surgery or any inflammatory kidney surgery, have kidney cancer associated with the urinary collection system, and have other kidney diseases (including kidney stones and glomerulonephritis).

5. Experimental program

5.1 The patients are screened according to the inclusion and exclusion criteria. Then the patients are divided into two groups according to whether they underwent zero-ischemic enucleation or partial nephrectomy, with the zero-ischemic enucleation group as the test group and the partial nephrectomy group as the control group. Describing the preoperative conditions(age, sex, Anatomy of tumor, RENAL score, ABC score, preoperative renal function), the perioperative conditions(operation time, intraoperative bleeding, perioperative complications, negative/positive specimen margins, postoperative renal function changes, postoperative hospitalization days), and the postoperative condition(follow-up renal function, tumor recurrence rate, overall survival, tumor-free survival, progression-free survival).

5.2 The data of the two groups are corrected for baseline and screened so that there is no statistical difference in the number of patients, gender age, tumor anatomy, renal function and other preoperative conditions between the two groups (t-test/rank sum test $p > 0.05$).

5.3 The zero ischemic renal enucleation group is grouped according to RENAL score, ABC score and other scoring criteria. Different preoperative tumor score groupings are used as exposure

factors, and the percentage decrease of postoperative renal function compared with preoperative, perioperative complication rate and postoperative survival rate are used as outcome variables to analyze the association between exposure factors and outcome, to investigate the association of different factors on the surgical outcome of zero ischemic renal enucleation.

5.4 Using zero-ischemic nephrectomy or partial nephrectomy with clamping of the renal hilum as the exposure factor. T-test/rank sum test and one-way regression are used to compare the efficacy indexes such as negative/positive tumor margins, postoperative and follow-up renal function, survival rate, and safety indexes such as perioperative complication rate and intraoperative bleeding between the two groups to investigate whether there is a statistical difference in their treatment safety and efficacy. Then we investigated whether there are statistical differences and correlations between the safety and efficacy of the treatment, and whether there are statistical differences in survival outcomes between the two groups by multifactorial cox regression.

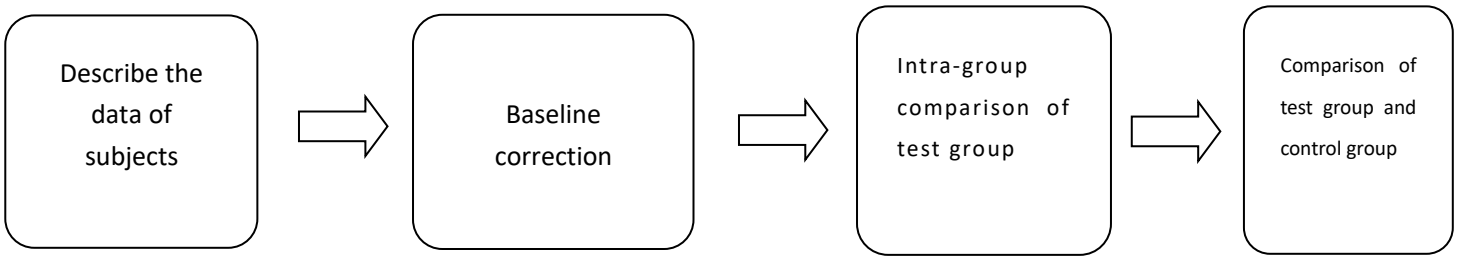

Figure 2. Experimental flow

6. Data management and statistical analysis

6.1 Statistical Software

Data statistics are processed by biostatisticians using the statistical software SPSS 20.0.

6.2 Data description

The measurement data are described as mean standard

deviation (x ± s), median, maximum, minimum, and quartiles, and the count data are expressed as percentages (%).

6.3 Statistics

Data entry: Enter the age, gender, kidney cancer stage and prognosis follow-up of the subjects.

Data management: The data are presented by number, and all personnel except the initial data entry personnel do not have access to the subjects' initial information (including subjects' personal information such as subjects' names, addresses, occupations and other sensitive information). There is no direct contact between the data entry personnel and the subjects, and all privacy of the subjects is protected from disclosure.

All hypothesis tests are two-sided, and differences are considered statistically significant at $P < 0.05$. Baseline data are evaluated for comparability between groups, and two-tailed statistical tests are performed at the a=5% level. The chi-square test or Fisher's exact probability method is used for comparison between groups for count data, the t-test for comparison between groups for measurement data, and the rank sum test for comparison between groups for nonparametric variables.

7. Informed consent

Previous case information is used for this study and a waiver of informed consent is requested.