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Postoperative immune response and surgical stress in selective neck dissection: Comparison between endoscopically assisted dissection and open techniques in cT1-2N0 oral squamous cell carcinoma

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ABSTRACT

Background: Endoscopically assisted selective neck dissection (SND) has recently been applied in clinical N0 cases of oral squamous cell carcinoma (OSCC). However, nothing is known of the immune response after surgery.
Methods: A total of 60 patients with cT1-2N0 OSCC randomly underwent endoscopically assisted SND and open operations. The serum levels of IL-6, IL-8, IL-10, IL-1b, TNF-a, CRP, cortisol, ACTH, and growth hormone were analyzed before the start of the surgery (T0) and at 2 (T1), 6 (T2), 24 (T3), and 72 h (T4) after surgery.
Results: A total of 31 patients were randomized for endoscopic SND, whereas 29 underwent open procedures. The release of IL-6, IL-10 and CRP was significantly lower in the endoscopic group than in the open surgery group ($p < 0.05$), and cortisol levels were also lower in the endoscopic group ($p < 0.05$).
Conclusions: Endoscopic SND could effectively provide lower inflammatory responses and surgical stress, reducing peri-operative trauma and accelerating recovery.

1. Introduction

An increasing number of studies have demonstrated that surgical trauma causes a host inflammatory reaction or disturbs the immunological balance (Lenz et al., 2007; Veenhof et al., 2012; Wang et al., 2012; Narita et al., 2013). Under surgical stress and immune compromise, pro- and anti-inflammatory cytokines are released, and systemic inflammatory response syndrome can result in post-operative morbidity and adverse effects such as fever and pain, as well as cardiopulmonary, infective, and thromboembolic complications (Herzum and Renz, 2008; Veenhof et al., 2012). In certain severe forms, the systemic inflammation can cause failure of one or several vital organs (Dewar et al., 2009) because surgical trauma-induced endocrine and metabolic changes are thought to mediate increased demands on organ function (Veenhof et al., 2012). Additionally, multiple organ dysfunction syndrome (MODS) can be a consequence of trauma after severe systemic inflammation. Several mechanisms have been proposed for the functional deficiencies of tumor-associated immune function in oral cancer patients (Jewett et al., 2006). Consequently, it might be advantageous to use a surgical technique with less immunological impact for oral squamous cell carcinoma (OSCC) treatment.

Interleukin-6 (IL-6) is a cytokine with both pro- and anti-inflammatory abilities. It is associated with surgical complications and is a predictor of morbidity after surgical intervention

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(Veenhof et al., 2012; Kvarnstrom et al., 2013). IL-6 is considered a poor prognostic factor in oral cancer, and its secretion is facilitated by the tumor microenvironment (Culig, 2013). IL-8 is a pro-inflammatory interleukin that is significantly higher in patients with OSCC than in patients with chronic periodontitis or healthy controls (Punyani and Sathawane, 2013; Lisa et al., 2014). IL-10 is an anti-inflammatory interleukin that plays an important role in the development of oral cancer (Yao et al., 2008). Interleukin-1β (IL-1β) is a critical mediator of chronic inflammation and is implicated in many cancers. IL-1β has been reported to promote malignant transformation and tumor aggressiveness in OSCC (Lee et al., 2015). Tumor necrosis factor (TNF)-α is pro-inflammatory and induces an acute phase reaction with local and systemic inflammation (Aggarwal et al., 2006). Increasing TNF-α is related to histological grading and clinical staging in OSCC (Krishnan et al., 2014). C-reactive protein (CRP) is perhaps the most well known acute phase reactant and is closely related to the inflammatory response, extent of tissue trauma, and activity of the immune reaction (Veenhof et al., 2012). Cortisol (Moris et al., 2014), adrenocorticotropic hormone (ACTH) (Tacconi et al., 2010) and growth hormone (Veenhof et al., 2012) are associated with surgical stress, which is widespread in clinical practice.

Laparoscopic rectectomies (Kvarnstrom et al., 2013), colectomies (Tsamis et al., 2012; Veenhof et al., 2012; Wang et al., 2012), and prostatectomies (Narita et al., 2013) are superior to open operations with respect to reducing the amount of intraoperative bleeding and relieving post-operative pain, thereby reducing the surgical stress reaction, improving pulmonary function, promoting post-operative rehabilitation, and decreasing the post-operative length of the hospital stay. Over the past 20 years, advancements in endoscopic and robot-assisted procedures have allowed alternative, smaller, or even complete avoidance of neck incisions in OSCC selective neck dissection (SND) (Kim et al., 2012; Lee et al., 2012; Tae et al., 2013; Byeon et al., 2014). These surgeries for SND are actually more invasive than traditional direct open neck approaches but produce desirable neck cosmesis at the cost of more soft tissue dissection, increased postoperative pain, and longer operative times (Kim et al., 2012; Lee et al., 2012; Tae et al., 2013). Recently, aiming to strike a balance between scarless surgery and minimal invasiveness, we first performed endoscopically assisted SND via a small submandibular approach, with satisfactory cosmetic results and minimal invasiveness, for patients with cT1-2N0 OSCC (Fan et al., 2014). However, whether our procedure produces minimal postoperative systemic immune response and surgical stress is unclear. To the best of our knowledge, there have been no studies focusing on the effects of endoscopic or robot-assisted SND on post-operative immune function in OSCC patients.

The objective of the present study was therefore to determine the effects of endoscopically assisted SND on the systemic inflammatory response and surgical stress in OSCC patients.

2. Materials and methods

A total of 60 patients with early-stage OSCC in the Department of Oral and Maxillofacial Surgery of Sun Yat-Sen Memorial Hospital, between August 2012 and March 2013, were enrolled in this prospective study (Chictr.org/cn, ChiCTR-TRC-11001335). The inclusion criteria were as follows: no diseases of the immune system, no history of operations on the neck and distant metastases, no pre-operative radiotherapy or chemotherapy, and an American Society of Anesthesiology (ASA) score of I through III. Patients who had distant metastasis at the time of diagnosis or recurrence of OSCC, were receiving other anti-cancer therapy, needed reconstruction of the primary site with free flap surgery, had a primary tumor in the midline area, or were not agreeable to providing blood samples were excluded.

The patients were randomly divided into two treatment groups: endoscopically assisted SND via a small submandibular incision, or open SND via a transcervical approach. The SND included level I, II, and III. All patients received general anesthesia with standardized anesthetic techniques. The surgical technique has been described in our previous study (Fan et al., 2014).

Peripheral blood and serum were collected at five different time points. The first sample (T0) was taken after the induction of anesthesia and before the start of the surgery (baseline). The second sample (T1) was taken 2 h after the start of surgery. The third sample (T2) was taken 6 h after the start of surgery. The fourth sample (T3) was taken 24 h after the start of surgery. The final sample (T4) was taken in the late postoperative period 72 h post-surgery. Serum samples for IL-6, IL-8, IL-10, IL-1β, TNF-α, CRP, cortisol, ACTH, and growth hormone analysis were obtained by centrifugation for 10 min at 3000 rpm at 4 °C. All samples were stored in aliquots at −80 °C until testing via a one-block design.

2.1. Immunologic parameters

The IL-6, IL-8, IL-10, IL-1β, and TNF-α concentrations in the serum were measured using commercially available chemiluminescence immunoassay kits (YZB/UK 2496-2011, YZB/UK 3068-2011, YZB/UK 1809-2011, YZB/UK 1812-2011, YZB/UK 2614-2012; Siemens Healthcare Diagnostics Products Limited, Gwynedd, UK). The serum CRP levels were measured via chemiluminescence immunoassay kits (YZB/GEM 4345-2012, Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany).

2.2. Stress response

The cortisol concentrations in the serum were measured by chemiluminescence immunoassay kits (YZB/USA 5709-2012, Siemens Healthcare Diagnostics Inc., Walpole, MA, USA). The ACTH and the growth hormone concentrations in the serum were measured by chemiluminescence immunoassay kits (L2KAC2, Siemens Healthcare Diagnostics Inc., Walpole, MA, USA) and (YZB/USA 4219-2012, Siemens Healthcare Diagnostics Inc., Los Angeles, CA, USA), respectively.

2.3. Statistical analysis

A visual analog scale (VAS) (Fan et al., 2014) was used to score postoperative pain. Statistical analyses were performed using the SPSS 19.0 package (SPSS, Chicago, IL, USA). The means, standard deviation (SD), and ranges were calculated and subsequently shown when appropriate. Chi-square tests, Mann–Whitney U tests, and analysis of variance (ANOVA) were applied for group comparisons when appropriate. A p value of <0.05 indicates statistical significance.

3. Results

3.1. Patients

A total of 31 patients were randomized for endoscopically assisted SND, whereas 29 patients underwent open SND. The patient characteristics in terms of age, sex, body mass index (BMI), ASA score, operative procedure, and treatment outcomes were comparable for both groups and are depicted in Table 1. There were no significant differences between the two groups regarding age, sex, BMI, or ASA score. No significant differences between the two groups were found for intraoperative blood loss and all

Table 1
Peri-operative data and treatment outcomes.

Variable	Endoscopic (n = 31)	Open (n = 29)	p
Age, mean (range), y	54.8 (26.5–66.6)	52.3 (31.4–64.9)	0.826
Sex, male:female	22:9	16:13	0.205
BMI, mean (range)	24.8 (19–27)	23.2 (20–27)	0.512
ASA score			0.744
I	9	11	
II	19	16	
III	3	2	
Length of incision [cm (range)]	4.1 (3.0–5.2)	15.4 (9.8–21.3)	<0.001
Operation time [min (range)]	114.6 (98.5–153.4)	73.5 (55.0–110.6)	<0.001
Intraoperative blood loss (ml)	54.8 (48.5–89.5)	60.7 (38.5–78.5)	0.327
Amount of drainage (ml)	165.8 (80.5–205.0)	213.2 (68.5–312.5)	0.043
Duration of drainage (days)	3.2 (2.0–4.5)	4.5 (3.5–6.5)	0.036
All complications			0.459
Numbness of earlobe	1	4	
Temporary mouth corner deviation	4	3	
Seroma/hematoma	0	1	
Wound infection	0	1	
Pneumonia	2	0	
Postoperative pain Score	4.5 (2.3–7.2)	6.8 (4.5–8.6)	0.019
Hospital stay (days)	6.9 (5.5–9.6)	8.2 (6.5–13.5)	0.006

BMI, body mass index; ASA, American Society of Anesthesiology.

complications. However, other surgical parameters and outcomes, including the length of incision, amount and duration of drainage, postoperative pain score, and hospital length of stay but not the duration of the operative procedure, indicated that endoscopically assisted SND was superior to open SND.

3.2. Immune status

Based on the total number of blood sample accrual times described by the protocol, a total of 60 patients should yield 2700 values based on nine cytokine and hormone measurements per patient at one time point. A total of 23/2700 (0.09%) values were missing, mainly due to time delays and improper sample preparation. Table 2 shows the means and ranges for each cytokine by both group and time point.

IL-6, IL-8, IL-10, TNF-α, and CRP are released during endoscopic and open SND. The post-operative IL-6 and CRP concentrations were significantly higher in the open group compared with the endoscopic group at T1, T2, T3, and T4 (Table 2; Fig. 1A and C), whereas the IL-10 (Table 2; Fig. 1B) and TNF-α (Table 2) changes were similar to the former at the early stages (T1, T2, and T3) and (T1 and T2) after surgery and then immediately decreased. The mean IL-6, IL-10, TNF-α, and CRP levels for the combined post-operative time intervals are given in Table 3. Only changes in IL-6, IL-10, and CRP showed significant differences between the two groups.

3.3. Stress response

By comparing the concentration changes in cortisol, ACTH, and growth hormone between the two groups, we found that only cortisol was significantly lower in the endoscopic group at T1, T2, and T3 (Table 2; Fig. 1D). The mean cortisol level for the combined postoperative time intervals also showed a significant difference, which is shown in Table 3.

4. Discussion

Surgical trauma and stress are very important for patients with malignant diseases, because it is well-known that abnormal postoperative immune activity may lead to an increased occurrence of post-operative infections and metastasis of tumor cells, as circulating tumor cells are at their highest concentrations directly after the onset of surgery (Wind et al., 2009). Therefore, numerous studies have suggested a biological substrate in response to the long-standing question of why cancer patients undergoing minimally invasive surgery have an accelerated recovery (Veenhof et al., 2012; Kvarnstrom et al., 2013; Narita et al., 2013) or even improved survival (Lacy et al., 2008; Novitsky et al., 2004).

In the field of head and neck surgery, the first endoscopically assisted operation was performed by Gagner (1996). Endoscopic techniques provide a magnified, illuminated, and adequate operative view, and the surgeon may consequently identify pertinent anatomy more easily and thus perform a meticulous surgical dissection. Recently, robotic or endoscopic surgeries for SND have been applied in cases of head and neck cancer, including OSCC, oropharyngeal cancer, and parotid cancer (Kim et al., 2012; Lee

Table 2
Mean (range) concentrations of inflammatory and hormone variables by type of surgery and time point.

Variable	Groups	T0 baseline	T1 2 h	T2 6 h	T3 24 h	T4 72 h
IL-6 (0–5.9 pg/ml)[a]	Endoscopic	2.9 (0.7–3.8)	**48.5 (32.8–73.2)**	**105.3 (98.1–168.9)**	**64.5 (27.6–109.2)**	**18.6 (9.3–43.7)**
	Open	2.5 (0.8–4.1)	**170.4 (108.7–225.1)**	**146.2 (93.2–196.2)**	**105.6 (76.2–166.7)**	**54.3 (21.4–76.1)**
IL-8 (0–62 pg/ml)[a]	Endoscopic	10.9 (3.4–21.5)	69.5 (41.5–98.6)	77.2 (39.7–89.8)	12.4 (2.3–19.8)	5.6 (1.7–10.6)
	Open	7.6 (4.6–16.4)	73.2 (39.5–103.6)	71.8 (46.2–96.4)	9.7 (3.5–16.5)	7.1 (2.6–13.2)
IL-10 (0–9.1 pg/ml)[a]	Endoscopic	3.2 (0.6–6.2)	**16.7 (10.6–36.7)**	**31.7 (18.9–62.7)**	**18.3 (9.4–29.4)**	5.6 (2.1–8.3)
	Open	2.4 (0.4–5.7)	**108.1 (56.8–168.5)**	**67.5 (41.5–92.7)**	**34.6 (23.4–45.7)**	4.8 (1.3–6.7)
IL-1β (0–5 pg/ml)[a]	Endoscopic	2.2 (0.4–3.8)	3.8 (1.0–4.6)	2.6 (0.5–3.8)	3.7 (0.6–4.9)	2.4 (0.4–4.9)
	Open	2.7 (0.4–4.3)	4.2 (0.9–5.3)	3.2 (0.8–5.1)	4.5 (1.3–6.7)	1.9 (0.3–3.6)
TNF-α (0–8.1 pg/ml)[a]	Endoscopic	5.3 (3.2–8.4)	**9.7 (7.9–13.2)**	**8.6 (5.4–10.3)**	7.5 (5.2–9.3)	5.6 (2.3–8.0)
	Open	4.7 (2.8–8.6)	**14.3 (8.5–23.4)**	**12.6 (6.7–18.9)**	6.8 (3.7–9.2)	5.3 (3.1–7.2)
CRP (0–5 mg/L)[a]	Endoscopic	1.7 (0.2–3.6)	**14.2 (6.7–21.6)**	**31.8 (23.6–40.1)**	**53.3 (38.1–69.4)**	**49.8 (29.8–67.1)**
	Open	2.4 (0.4–4.8)	**23.9 (14.2–30.4)**	**50.7 (38.4–63.9)**	**86.2 (54.7–101.3)**	**153.4 (98.2–186.4)**
Cortisol (118.6–618 nmol/L)[a]	Endoscopic	459.7 (132.8–609.7)	**769.5 (629.7–804.5)**	**896.7 (648.3–912.5)**	**461.9 (120.9–583.6)**	506.4 (186.2–637.5)
	Open	436.2 (183.6–598.6)	**1006.1 (726.9–1352.4)**	**1276.8 (786.8–1420.6)**	**739.6 (559.8–913.6)**	493.6 (149.5–609.5)
ACTH (0–46 pg/ml)[a]	Endoscopic	23.9 (5.0–34.5)	45.7 (20.3–58.3)	38.2 (4.3–49.6)	26.1 (2.1–42.3)	23.4 (8.3–39.4)
	Open	16.3 (6.4–27.6)	51.6 (30.4–67.3)	43.5 (23.5–64.8)	31.6 (6.2–49.8)	19.8 (8.2–36.7)
Growth hormone (0–10 ng/ml)[a]	Endoscopic	5.2 (0.8–8.9)	6.4 (0.9–8.9)	9.6 (0.2–13.3)	8.9 (0.4–14.2)	4.3 (0.6–8.7)
	Open	4.2 (0.4–7.6)	5.9 (1.2–7.6)	12.6 (2.6–16.2)	5.6 (2.3–9.7)	2.6 (0.2–5.9)

IL, interleukin; TNF-α, tumor necrosis factor-α; CRP, C-reactive protein; ACTH, adrenocorticotropic hormone.
Values in bold indicate significant difference in concentration between the two treatment groups ($p < 0.05$).
[a] Normal value in healthy subjects.

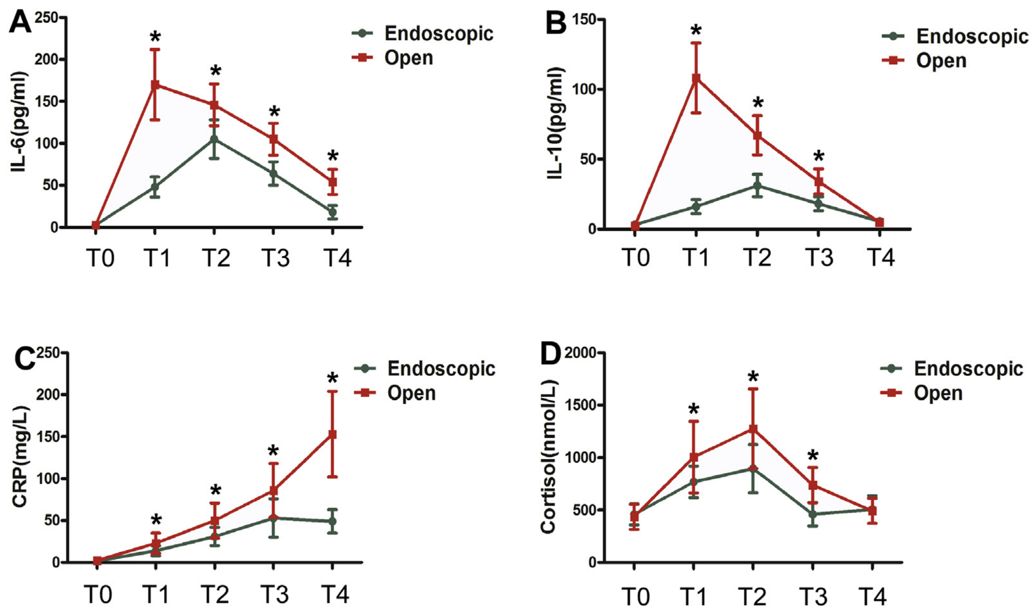

Fig. 1. Peri-operative changes in IL-6, IL-10, CRP, and cortisol, in all patients treated with endoscopic and open SND. *p < 0.05 for comparison between the two study groups. IL, interleukin; CRP, C-reactive protein; T0, before surgery; T1, postoperative 2 h; T2, postoperative 6 h; T3, postoperative 24 h; T4, postoperative 72 h; SND, selective neck dissection.

et al., 2012; Tae et al., 2013; Byeon et al., 2014). However, considering the surgical invasiveness and cosmetic results, controversies related to such procedures remain, due to the long distance from the incision to the dissection levels as well as certain postoperative complications (Fan et al., 2014). To achieve minimal surgical invasiveness and satisfactory cosmetic results, we first performed endoscopically assisted SND via a small submandibular approach in patients with OSCC (Fan et al., 2014).

The present study was not designed to investigate the differences in clinical parameters between the endoscopic and open surgery groups. Based on the operative and hospital data, we can safely state that endoscopically assisted SND was superior to open SND based on the length of incision and patient recovery. To date, no previous studies have investigated the immune status and stress response, which correspond to the observed cosmetic results and faster recovery from minimally invasive SND.

The present study shows that both pro- and anti-inflammatory cytokines are released during endoscopic and open SND. Our study also shows that significantly lower levels of IL-6, IL-10, TNF-α, and CRP are released in patients who undergo the endoscopic technique than in those who undergo open surgery. For the combined postoperative time intervals, IL-6, IL-10, and CRP were also significantly lower in the endoscopic group.

Table 3
Values (mean ± SD) for combination of post-operative time intervals.

Variable	Groups	Mean ± SD	p
IL-6 (pg/ml)	Endoscopic	59.2 ± 13.6	<0.001
	Open	119.1 ± 21.4	
IL-10 (pg/ml)	Endoscopic	18.1 ± 3.5	0.026
	Open	53.8 ± 16.8	
TNF-α(pg/ml)	Endoscopic	7.9 ± 1.6	0.472
	Open	9.8 ± 2.4	
CRP (mg/L)	Endoscopic	37.3 ± 13.6	0.006
	Open	78.6 ± 26.1	
Cortisol (nmol/L)	Endoscopic	658.6 ± 209.5	0.037
	Open	879.0 ± 312.9	

IL, interleukin; TNF-α, tumor necrosis factor-α; CRP, C-reactive protein.

IL-6 is considered a major mediator of the acute-phase protein response following injury or surgical invasion, and compared with other cytokines, the concentration of IL-6 is most consistently increased in the circulation of patients (Tsamis et al., 2012). The serum IL-6 level after laparoscopic operations was significantly reduced compared with the open technique for rectectomies, colectomies, and prostatectomies. CRP is an anon-specific acute-phase protein produced by the liver following trauma or inflammation. Indeed, the serum CRP level is increased in association with surgical trauma and stress (Wang et al., 2012). Therefore, measurement of the postoperative CRP level may reflect each surgical invasion and the degree of tissue trauma. Serum CRP levels after laparoscopic rectal surgery and colectomy have been shown to be significantly lower than those after open operations (Veenhof et al., 2012; Kvarnstrom et al., 2013). Bleeding is known to cause an inflammatory response. However, the intraoperative blood loss showed no significant difference between the two groups in the present study. We suggest that a possible explanation for the better immune preservation in endoscopically assisted SND is that the surgeon performed a very short incision and achieved an accurate identification and meticulous dissection. Consequently, patients in the endoscopic group had less drainage and experienced less postoperative pain and a shorter hospital stay.

The complex interaction between inflammatory cytokines and the sympathetic/adrenomedullary system or hypothalamic-pituitary-adrenal axis is still difficult to assess (Veenhof et al., 2012; Moris et al., 2014). The simultaneous activation of these two systems allows the organism to adapt and to maintain or regain homeostasis during surgical stress. In the present study, we found that the postoperative levels of cortisol were lower in the endoscopic group than in the open group, which was also consistent with other studies of major abdominal surgery (Kataja et al., 2007). ACTH has been shown to be associated with high cortisol following major surgery in general (Dimopoulou et al., 2008). However, we did not find any significant difference between the two types of surgery postoperatively. No significant difference was found between the two groups in the current study regarding growth hormone levels, and Veenhof et al. (2012) also found that the postoperative levels of growth hormone could be attributed to the type of aftercare but not the surgical procedure in colectomies. Therefore, the two types of procedure in the present study may cause the release of different levels of cortisol, but not of ACTH and growth hormone. However, their metabolized products may be interesting to evaluate in a future study.

Finally, considering immune maintenance and the lower level of surgical stress in minimally invasive surgery, the ambiguous viewpoints regarding port-site tumor recurrence, slow adoption of the method, and oncologic equivalency with its open counterpart have been well proved in randomized trials in colon and rectal cancer patients (Barlehner et al., 2005; Buunen et al., 2009). In our previous study, patients in the two groups did not present with any significant difference in regional metastasis during approximately 3 years of follow-up. However, whether the extent of the surgical trauma and its immunological consequences really has an impact on the oncological safety and patient survival is not fully known and requires further investigation.

5. Conclusion

The pro- and anti-inflammatory responses and surgical stress for SND were lower in endoscopic surgery than in the open procedure. This study is the first to reveal that endoscopically assisted SND via a small submandibular approach protects the postoperative immune system and yields accelerated recovery. The study further demonstrates that this procedure could reduce surgical trauma and provide minimal invasiveness. However, further studies are needed to investigate the long-term outcomes, oncological safety, and patient survival.

Conflict of interest

The authors declare no conflict of interest.

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