



## Kidney Cancer

# Laparoendoscopic Single-Site and Conventional Laparoscopic Radical Nephrectomy Result in Equivalent Surgical Trauma: Preliminary Results of a Single-Centre Retrospective Controlled Study

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## Abstract

**Background:** Laparoendoscopic single-site surgery (LESS) has been developed in an attempt to further reduce the morbidity and scarring associated with surgical intervention, and it has been proposed to result in less induced surgical trauma than conventional laparoscopy.

**Objective:** Investigate the surgical trauma after LESS radical nephrectomy (LESS-RN) and laparoscopic radical nephrectomy (LRN).

**Design, setting, and participants:** This was a retrospective single-centre study including 66 patients: 31 patients underwent LESS-RN and 35 historical control patients who had undergone LRN. LRNs were performed between April 2008 and May 2009; LESS-RNs were performed between May 2009 and February 2011.

**Intervention:** LESS-RN and LRN were both performed via a transperitoneal access. Blood samples were collected pre- and intraoperatively at 6, 24, and 48 h, and at 5 d postoperatively.

**Measurements:** Serum concentrations of acute-phase markers, C-reactive protein (CRP), serum amyloid A (SAA) antibody, and interleukin 6 (IL-6) and interleukin 10 (IL-10) were measured at each time point by enzyme-linked immunosorbent assay. Clinical data were collected by reviewing the patient's records.

**Results and limitations:** There were no differences in serum CRP and SAA levels between the groups (CRP:  $p = 0.12$ ; SAA:  $p = 0.09$ ) at all time points. The changes in IL-6 levels in the LRN group were statistically significantly higher compared with the LESS-RN group at 6 h after surgery ( $p = 0.02$ ), whereas the LESS-RN group showed statistically significantly higher IL-6 levels than the LRN group at 24 h after surgery ( $p = 0.02$ ).

Also, the serum levels of the anti-inflammatory cytokine IL-10 showed different kinetics in each group, being higher in the LESS-RN during the early postoperative phase (at 6 h:  $p = 0.01$ ) and higher in the LRN group at 48 h after surgery ( $p = 0.01$ ). The limitations of this study were its nonrandomized character and the small cohort of patients.

**Conclusions:** LESS-RN is as effective as LRN without compromising surgical and postoperative outcomes, but it does not add any significant advantage in comparison with traditional LRN in terms of systemic stress response and surgical trauma.

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## 1. Introduction

Major urologic surgical procedures cause a systemic inflammatory reaction: tissue damage caused by surgical trauma and anaesthesia-related interventions leads to local activation of various cells (eg, monocytes and macrophages) that release cytokines and other mediators [1]. This activation may be followed by a systemic acute-phase reaction, which is proportional to the extent of tissue damage [2]. However, tissue damage from abdominal surgery may also result in postoperative fatigue and affect various organ systems with the possibility of organ failure [1,2].

The advent of laparoscopy has greatly influenced urologic surgery. The reduced surgical invasiveness is thought to preserve immune function after surgery because of smaller incisions, reduced tissue injury, and less blood loss [3]. Decreased perioperative stress is particularly important when performing oncologic surgery, as exaggerated activation or reactive suppression of the immune system can affect tumour growth and dissemination.

The physiologic response to acute stress induced by major surgical interventions involves finely integrated interactions between the autonomic nervous, endocrine, and immune systems, and metabolism. In particular, numerous studies have focused on the activation of the endocrine stress response, which includes the activation of the hypothalamic-pituitary-adrenal axis, the sympathetic medullary system, and their modulators [1,4–7].

Laparoendoscopic single-site surgery (LESS) has been developed in an attempt to further reduce the morbidity and scarring associated with surgical intervention. The LESS approach is a new and rapidly expanding arena of clinical and basic research across many surgical disciplines. Early interest from the medical and corporate worlds has led to escalating clinical applications within a rather short period.

While the minimal invasiveness of laparoscopy, compared with open surgery, has been demonstrated [3], no study to date has established that LESS results are less invasive compared with conventional laparoscopy.

In the present study, we investigated the changes in perioperative release of known inflammatory markers and cytokines—C-reactive protein (CRP), serum amyloid A (SAA), interleukin (IL) 6, and IL-10—in patients undergoing LESS radical nephrectomy (LESS-RN) and conventional laparoscopic radical nephrectomy (LRN), exploring if LESS-RN really presents reduced surgical trauma as a consequence of the reduced number of skin incisions compared with LRN.

## 2. Material and methods

This was a retrospective single-centre study including 66 patients recruited between April 2008 and February 2011: 31 patients underwent LESS-RN and 35 historical control patients had undergone LRN. LRNs were performed between April 2008 and May 2009; LESS-RNs were performed between May 2009 and February 2011. The study was approved by the institutional review board. Written informed consent was obtained from all patients.

Both groups included the initial series of patients who underwent a LESS-RN or LRN performed by the same surgeon (F.G.) to avoid the bias presented by the surgical learning curve.

The indications to perform a LESS-RN and a LRN were represented by renal tumours grade T2 or lower without evidence of lymphadenopathy or renal vein involvement and absence of health conditions precluding a laparoscopic procedure.

Patients included in the study were not eligible for partial nephrectomy (infiltration of the renal vessels and/or of the pelvicalyceal system) or had decided to undergo a radical procedure to reach oncologic safety.

The following information was collected: age; gender; ethnicity; body mass index (BMI); preoperative conditions (ie, smoking status, diabetes, renal insufficiency, hypertension); pre- and postoperative renal function; specific comorbidities; American Society of Anaesthesiologists (ASA) score; tumour stage and grade; surgical margin status; specimen weight; operative time; and estimated blood loss. Additional collected data included pre- and postoperative serum haemoglobin levels; transfusion data; conversion to open surgery or to standard laparoscopy; length of stay (LOS); postoperative pain assessed using a visual analogue scale (VAS) score at discharge; incision length; and subjective scar satisfaction.

Patients were excluded if they had comorbidities resulting in raised inflammatory marker levels (eg, autoimmune disease, diabetes mellitus, infection, or intra- and postoperative complications).

The RENAL (tumour radius, exophytic or endophytic properties, nearness to the renal sinus fat or collecting system, anterior or posterior position, and polar vs nonpolar location) nephrometry score was used to assess the characteristics of the tumours in both groups [8].

Total intravenous general anaesthesia was induced and maintained with sufentanil and propofol in all groups. No anaesthetic gases were used. After relaxation with pancuronium bromide, the trachea was intubated, and controlled normocapnic ventilation with an air-oxygen mixture was started. No patients received corticosteroids before, during, or after surgery. Our surgical techniques were described in detail elsewhere [9,10].

At the first postoperative visit, all patients completed a subjective questionnaire, rating the cosmetic results as: 1: dissatisfied; 2: satisfied; 3: very satisfied; or 4: enthusiastic.

### 2.1. Study protocol

Patients were recruited the day before surgery and venous blood was drawn for baseline measurements of biochemical serum parameters and plasma cytokine levels. All baseline blood samples were collected in ethylenediamine tetra-acetic acid-containing tubes in the morning between 0900 and 1200 h (time point T0). Intraoperatively, serial blood samples were collected from the venous line after the placement of the trocar(s) and after removing the specimen (time points T1 and T2). After surgery, all patients were transferred to the ward and serial blood samples were collected from the venous line at 6, 24, and 48 h, and at 5 d after surgery (time points T3, T4, T5, and T6). Plasma was recovered immediately from all samples and aliquots were frozen at  $-80^{\circ}\text{C}$  until final use.

### 2.2. Measurements

As part of the routine clinical observations, selected clinical and biochemical data were recorded at each time point. Acute-phase protein, CRP, and SAA antibody levels were determined using highly sensitive nephelometric assays (Dade Behring Co., Marburg, Germany). Inflammatory cytokine analyses were performed as follows: Samples were assayed in a single large batch, duplicates agreed within 15%, and quality assessment samples were within the manufacturer's defined range. Enzyme-linked immunosorbent assay techniques were applied to determine levels of IL-6 (proinflammatory cytokine), and anti-inflammatory cytokine IL-10 (IBL, Hamburg, Germany). The intra- and

interassay coefficients of variation were <10% and 7.4% for IL-10, and 5.2% and 3.4% for IL-6, respectively. The plasma hormone and cytokine concentrations at each time point (T) were corrected for haemodilution according to the following formula:

$$\text{Marker level (corrected)} = \frac{\text{Marker level (measured)} \times \text{haematocrit (baseline)}}{\text{haematocrit (T)}}$$

The mean correction factors were  $1.15 \pm 0.21$  (LESS-RN group) and  $1.28 \pm 0.42$  (LRN group).

### 2.3. Statistical analysis

Statistical analysis was performed using SigmaPlot software v.11.0 (IBM Corp., Armonk, NY, USA). Data are expressed as the mean plus or minus standard error of the mean (SEM) or percentage of baseline, and statistical significance was accepted at  $p < 0.05$ . Fisher exact test was applied to evaluate statistical between-group differences in pathologic stages. Inflammatory-marker levels were analysed by the repeated measures two-way analysis of variance (ANOVA). Repeated measurement post hoc between-groups effects were evaluated by the Tukey test. Within-group effects for time were tested by post hoc Dunnett contrasts of baseline values versus subsequent measurements. Pearson's correlation analysis was used to determine relationships between members of the inflammatory cascade and acute-phase proteins. The sample size was based on the differences in IL-6 levels at 24 h postoperatively using an effect size of 1.0, an alpha level of 0.05, and a power of 0.80. The determination of the sample size and effect size was appropriate for the number of treatment groups in this type of research and was consistent with previously published guidelines [11].

## 3. Results

### 3.1. Preoperative outcomes

Preoperative results are summarized in Table 1.

Two patients from the LESS group and three from the LRN group were excluded from the analysis for the presence of comorbidities that could result in raised inflammatory-marker levels.

The patient population was generally young (mean age:  $54.2 \pm 15.3$  yr in the LESS-RN and  $57 \pm 14.2$  yr in the LRN groups;  $p = 0.13$ ), not obese (mean BMI:  $27.3 \pm 2.4$  kg/m<sup>2</sup> in the LESS-RN and  $27.9 \pm 1.3$  kg/m<sup>2</sup> in the LRN groups;  $p = 0.15$ ),

**Table 1 – Preoperative data of laparoendoscopic single-site radical nephrectomy (LESS-RN) versus laparoscopic radical nephrectomy (LRN)**

	LESS-RN	LRN	p value
Patients, no.	31	35	–
Age, yr	$54.2 \pm 15.3$	$57 \pm 14.2$	0.132
Gender ratio (female/male)	1.8	1.25	0.095
BMI, kg/m <sup>2</sup>	$27.3 \pm 2.4$	$27.9 \pm 1.3$	0.122
Left/right kidney	23/8	23/12	0.097
Preoperative tumour size, cm	$4.9 \pm 1.9$	$5.4 \pm 1.9$	0.109
Mean ASA score	$2.2 \pm 1.4$	$2.3 \pm 0.7$	0.128

BMI = body mass index; ASA = American Society of Anaesthesiologists.

and healthy (mean preoperative ASA scores:  $2.4 \pm 1.6$  and  $2.5 \pm 0.7$ , respectively). Furthermore, none of the patients included in this study presented with diabetes, renal insufficiency, or hypertension, or was on statin therapy.

All patients underwent radical nephrectomy (RN) for enhancing renal masses with a median preoperative tumour size of  $4.9 \pm 1.9$  cm in the LESS-RN and  $5.4 \pm 1.9$  cm in the LRN groups.

### 3.2. Intra- and postoperative outcomes

The mean operative time in the LESS-RN group was  $139.9 \pm 26.1$  min versus  $130.6 \pm 26.5$  min in the LRN group ( $p = 0.112$ ). The mean LOS in the LESS-RN group was  $3.8 \pm 0.8$  d versus  $4.2 \pm 1.4$  d in the LRN group ( $p = 0.067$ ).

The mean length of the skin incision to extract the kidney in the LESS-RN group was  $4.1 \pm 0.6$  cm versus  $6.5 \pm 2.2$  cm in the LRN group ( $p = 0.046$ ; Table 2).

The definitive pathologic results revealed a renal cell carcinoma in all cases with a stage distribution of 2 T1a, 27 T1b, and 2 T2 in the LESS group and a stage distribution of 31 T1b and 4 T2 tumours after LRN (Table 3) [8].

The mean RENAL nephrometry scores for LESS-RN and LRN were  $9.28 \pm 1.3$  and  $9.32 \pm 0.7$  ( $p = 0.132$ ), respectively.

All the patients who underwent LESS-RN were enthusiastic about the appearance of their scars, whereas only 26 patients of the LRN group (74.3%) were enthusiastic ( $p = 0.0312$ ). At a median follow-up of  $13.2 \pm 3.9$  mo for

**Table 2 – Intraoperative and postoperative data of laparoendoscopic single-site radical nephrectomy (LESS-RN) versus laparoscopic radical nephrectomy (LRN)**

	LESS-RN	LRN	p value
Patients, no.	31	35	–
Operating time, min	$139.9 \pm 26.1$	$130.6 \pm 26.5$	0.112
Blood loss, ml	$120.6 \pm 37.3$	$130 \pm 62.71$	0.054
Transfusion rate, %	3.2	5.7	0.068
Haemoglobin decrease, mmol/l	$1.7 \pm 0.5$	$1.6 \pm 0.8$	0.128
Creatinine increase, $\mu$ mol/l	$13.3 \pm 7.8$	$14.7 \pm 6.9$	0.106
Postoperative day of oral intake	1.0	$1.3 \pm 0.3$	0.103
Mean VAS	$1.9 \pm 0.8$	$3.3 \pm 1.6$	0.041
Mean analgesic requirement, mg	$9.8 \pm 6.2$	$13.9 \pm 5.1$	0.021
Length of stay, d	$3.8 \pm 0.8$	$4.2 \pm 1.4$	0.067
Skin incision length, cm	$4.1 \pm 0.6$	$6.5 \pm 2.2$	0.046
Mean convalescence, d	$15.3 \pm 4.6$	$21.8 \pm 5.1$	0.052
Patients with tumour recurrence and port-site metastasis, no.	0	0	NA

VAS = visual analogue scale.

**Table 3 – Postoperative histopathologic results of laparoendoscopic single-site radical nephrectomy (LESS-RN) versus laparoscopic radical nephrectomy (LRN)**

	LESS-RN	LRN	p value
Patients, no.	31	35	–
Kidney weight, g	467.6 ± 111.2	482.4 ± 111.6	0.089
Specimen size, cm	11.7 ± 1	12.1 ± 0.9	0.112
Tumour stage			
pT1a	2	–	0.130
pT1b	27	31	0.098
pT2	2	4	
Fuhrmann tumour grade			
I	2	1	0.312
II	3	8	0.087
III	26	26	0.231
Tumour size, cm	5.7 ± 1.2	5.8 ± 1.4	0.131
Tumours, no./case	2/2	2/1	0.201
	1/29	1/34	0.134
Mean RENAL nephrometry score	9.28 ± 1.3	9.32 ± 0.7	0.132
Surgical margins	Negative	Negative	–

the LESS-RN group and of 21.3 ± 2.1 mo for the LRN group, all patients were alive with no evidence of tumour recurrence or port-site metastasis.

**3.3. Evaluation of the inflammatory markers**

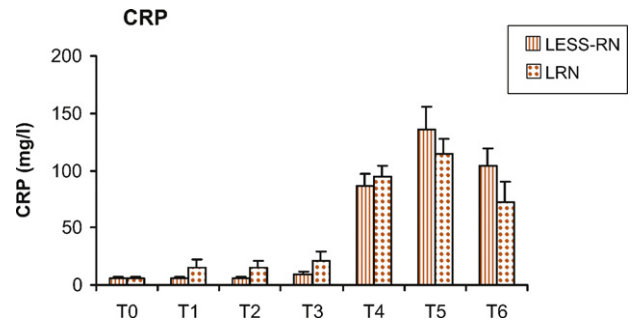
For the measures of the systemic response, there was an increase in the level of CRP detected 24 h after surgery, with a further increase of >100 mg/l at 48 h, but there were no differences in serum CRP levels between the treatment groups (*p* = 0.12; Fig. 1). Similarly, there was no relevant increase in SAA levels until 6 h after surgery, but at 24–48 h after surgery, there was a clear increase in the level of SAA in both treatment groups, although there was no difference between the groups (*p* = 0.09; Fig. 2).

Serum levels of proinflammatory cytokine IL-6 increased during the operation and in the early hours after the operation, reaching peak values at 24 h postoperatively (Fig. 3). Thereafter, they declined gradually, but remained above the baseline values up to 5 d after surgery. The changes in IL-6 levels in the LRN group were statistically significantly higher compared with the LESS-RN group at 6 h after surgery (*p* = 0.02), whereas the LESS-RN group showed statistically significantly higher IL-6 levels than LRN group at 24 h after surgery (*p* = 0.02), as evaluated by repeated-measures ANOVA.

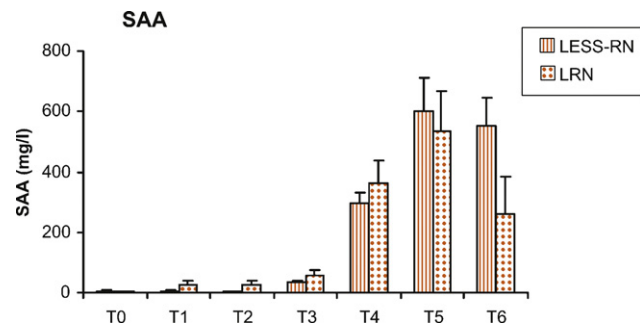
Also, serum levels of anti-inflammatory cytokine IL-10 showed different kinetics in each group, with these being higher in the LESS-RN group during the early phase (T2; *p* = 0.01) and higher in the LRN group at 48 h after surgery (T5; *p* = 0.01) (Fig. 4).

**4. Discussion**

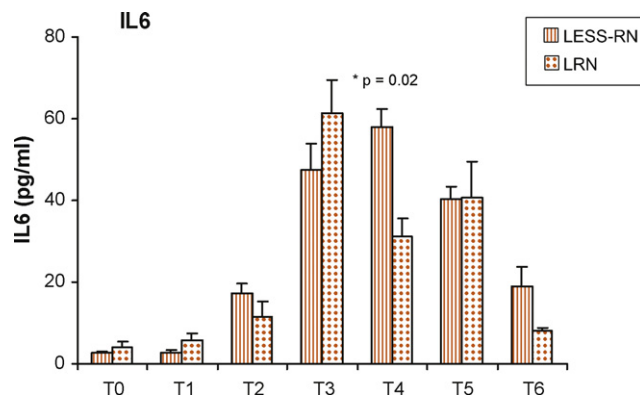
Minimally invasive surgery aims to provide effective treatment while decreasing access-related morbidity with a reduction in postoperative pain, shorter LOS, faster recovery, improved cosmesis, and early return of patients to their occupations [3,10].



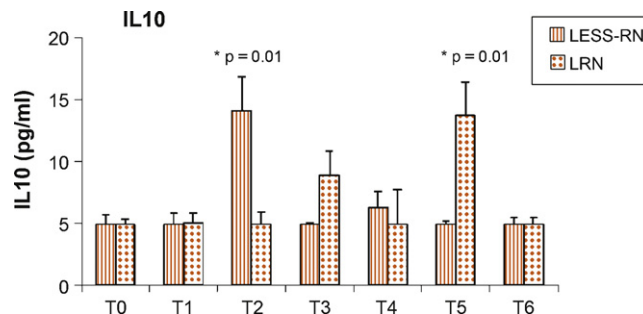
**Fig. 1 – Course of the C-reactive protein (CRP) at different time points.**



**Fig. 2 – Course of the serum amyloid A antibody (SAA) at different time points.**



**Fig. 3 – Course of interleukin 6 (IL-6) at different time points.**



**Fig. 4 – Course of interleukin 10 (IL-10) at different time points.**

LESS has been developed in an attempt to further reduce the morbidity and scarring associated with surgical intervention [12–15].

The first two large series of urologic LESS were published in 2009 [16,17]. Since then, other early single-centre experiences have been reported, albeit limited by small numbers, nonrandomised design, and lack of standardisation in the assessment of postoperative outcomes [18]. Overall, these series suggested that LESS was not inferior to conventional laparoscopy for perioperative outcomes, and revealed an encouraging trend toward less postoperative pain and better cosmesis [13,14,18].

As a general principle, all patients eligible for laparoscopic surgery may be considered for LESS. However, although performed by experienced laparoscopic surgeons, patient selection with LESS is more rigorous than with conventional laparoscopy and the threshold for conversion is low [19,20].

When considering the overall population of the present study, the patients were relatively young, not obese, and of low surgical risk. LESS-RN was as safe as LRN and no complications occurred in either group. Moreover, the intra- and postoperative oncologic outcomes did not present any statistical significant differences between groups.

When reducing the number of skin incisions from as many as four for LRN to only one for LESS-RN, it could be postulated that LESS is less invasive compared with conventional laparoscopy, but to date there has been no study that investigated if the true benefits of LESS are only restricted to an improved cosmesis, or if there are also benefits with respect to surgical trauma, namely, convalescence and postoperative recovery.

The surgical trauma-induced inflammatory response is well defined in the literature [1,2,4,10,21–27]. Primarily, the physiologic response to surgical trauma is equal to that of infection or injury, that is, the induction of the acute-phase response as reflected in cytokine function and cellular messenger systems [22]. The magnitude of these changes is reflected proportionally to the extent of the surgical trauma. Many studies support LRN as the gold standard over the traditional open approach based on results demonstrated by cytokine response profiles [2,10,23]. The perioperative secretion of cytokines is the result of several processes that occur during surgery: immunomodulatory effects of anaesthesia and drugs administered perioperatively, tissue damage, and the likelihood of endotoxaemia. Several studies have described an increase in blood levels of IL-6 in patients undergoing major surgery [1,4,10,21–27]. IL-6 is recognised as an early and robust marker of the systemic inflammatory response following surgery.

In 2001, Fornara et al, in a prospective, controlled, nonrandomised, animal and patient study, attempted to develop a method for quantifying tissue damage from various operative procedures [10]. To deal with the complexity of the acute-phase reaction, the proinflammatory cytokine IL-6 and the modulatory cytokine IL-10 were examined. In addition, CRP, as an important acute-phase protein, was measured [10]. The study showed that the

benefits of LRN compared with open RN for minimal invasiveness were evident.

Cruickshank et al. reported that the amount of IL-6 secretion in surgical patients has a positive correlation with the extent of surgical injury [25]. In accordance with the present results in a urologic surgery population, they described increased blood levels of IL-6 with peak levels 6–12 h after incision in patients undergoing abdominal surgical procedures. However, peak levels of IL-6 were also found in the present study's participants in the postoperative period. On the first postoperative day, IL-6 was maximally elevated compared with the preoperative values, reaching a higher peak, with statistically significant differences, at 6 h after surgery in the LRN group and at 24 h after surgery in the LESS-RN group than in LRN group.

In the present study, surprisingly, no statistically significant differences were reported for the other inflammatory markers, with CRP and SAA presenting a similar course in both groups and with IL-10 showing different higher values in the LESS-RN group during the early postoperative phase and in the LRN group at 48 h after surgery. The reason why the interleukins reached their peak in both groups at different times is not clear. In the literature it is only known that proinflammatory cytokines reach their maximal peak within 24 h of the inflammatory response, which also occurred in our study [28]. Unfortunately, the exact mechanisms and details of this cytokine response are not fully understood and only little literature is available on this topic [21,22].

According to these results, we could hypothesize that the increase in stress parameters is associated with the trauma to muscles, but it is not directly correlated with the sum of each single incision. Given that LESS-RN and LRN are different forms of the same minimal invasive technique, the only difference between these surgical procedures is the number of ports that are used; the extension of trauma to muscles is comparable for both techniques. This can explain the course of the cytokines in our study and the absence of any statistically significant difference in the measurements of the surgical trauma in both groups.

The limitations of this study were its retrospective, nonrandomised nature and the small cohort of the patients to show statistical differences between groups. Nevertheless, the power analysis justified the cohorts as large enough to find significant differences for inflammatory markers.

## 5. Conclusions

LESS-RN is as effective as LRN without compromising surgical and postoperative outcomes, but it does not add any significant advantage in comparison with traditional LRN in terms of systemic stress response and surgical trauma.

Despite promising early outcomes, the benefits of LESS are not obvious at present, with the only claimed advantage being cosmetic.

**Author contributions:** Francesco Greco had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Greco.

*Acquisition of data:* Greco, Springer, Fischer, Mohammed.

*Analysis and interpretation of data:* Greco, Hoda, Fischer.

*Drafting of the manuscript:* Greco.

*Critical revision of the manuscript for important intellectual content:* Greco, Fornara.

*Statistical analysis:* Hoda, Fischer.

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*Supervision:* Fornara.

*Other (specify):* None.

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