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Redo Partial Nephrectomy for Local Recurrence After Previous Nephron-sparing Surgery. Surgical Insights and Oncologic Results from a High-volume Robotic Center

Fabrizio Di Maida[a,*], *Antonio Andrea Grosso*[a], *Riccardo Campi*[b], *Luca Lambertini*[a], *Maria Lucia Gallo*[b], *Anna Cadenar*[a], *Vincenzo Salamone*[a], *Simone Coco*[a], *Daniele Paganelli*[a], *Agostino Tuccio*[a], *Lorenzo Masieri*[b], *Andrea Minervini*[a]

[a] *Unit of Oncologic Minimally Invasive Urology and Andrology, Department of Experimental and Clinical Medicine, Careggi Hospital, University of Florence, Florence, Italy;* [b] *Unit of Urological Robotic Surgery and Renal Transplantation, Department of Experimental and Clinical Medicine, Careggi Hospital, University of Florence, Florence, Italy*

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Abstract

Background: The role of redo partial nephrectomy (PN) for recurrent renal cell carcinoma (RCC) is still overlooked.
Objective: To report our experience of salvage PN for local recurrence after previous nephron-sparing surgery (NSS).
Design, setting, and participants: We prospectively gathered data from patients treated with robotic redo PN for locally recurrent RCC after previous NSS from January 2017 to January 2023. The type of surgical resection technique was assigned to the pathologic specimen according to the surface-intermediate-base (SIB) score.
Surgical procedure: Redo PN was performed by using the Si Da Vinci robotic platform.
Measurements: Operative time, warm ischemia time, and intra- and postoperative complications were recorded. The severity of postoperative complications and tumor stage were evaluated.
Results and limitations: Overall, 26 patients entered the study. The median clinical diameter was 3.5 (interquartile range [IQR] 2.2–4.9) cm and the median Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) score was 8 (IQR 7–9). In 14 (53.8%) cases, recurrence was at the level of previous tumor resection bed. The median operative time was 177 (IQR 148–200) min, and hilar clamping was performed in 14 (53.8%) cases with a median warm ischemia time of 16 (14.5–22) min. Pure enucleation (SIB score 0–1), hybrid enucleation (SIB score 2), and pure enucleoresection (SIB score 3) were recorded in 13 (50%), eight (30.8%), and five (19.2%) cases, respectively. The totality of recurrent RCC far from previous tumor resection bed received a SIB score of 0–1, while in 57.1% and 35.8% of

* Corresponding author. Unit of Oncologic Minimally Invasive Urology and Andrology, Department of Experimental and Clinical Medicine, Careggi Hospital, University of Florence, Largo Brambilla 3, Florence 50134, Italy. Tel. +393334335984; Fax: +390557942000.
E-mail address: fabrizio.dimaida@unifi.it (F. Di Maida).

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recurrent RCC on previous tumor resection a hybrid enucleation and a pure enucleoresection were performed, respectively. At a median follow-up of 37 (IQR 16–45) mo, five (19%) patients experienced disease recurrence, being local and systemic in three (11.5%) and two (7.7%) patients, respectively.
Conclusions: Our study highlights the feasibility and safety of redo PN for the treatment of locally recurrent RCCs after NSS, either on previous tumor resection bed or elsewhere in the kidney.
Patient summary: Robotic redo partial nephrectomy is a challenging procedure. The surgeon needs to tailor the surgical strategy and tumor resection technique case by case, given the heterogeneity of clinical scenarios and the need to achieve maximal functional preservation while ensuring oncologic efficacy.

1. Introduction

The past decade has been characterized by a profound evolution in the treatment of renal cell carcinoma (RCC). Indeed, over the past years a paradigm shift toward partial nephrectomy (PN) was observed in the management of clinical T1b and, more recently, T2 renal masses [1,2]. As a result, while surgically treated cT1 RCCs generally show a good prognosis, concerns have been raised with respect to utilization of PN for larger or complex masses also due to a hypothetical higher risk of tumor relapse. Local recurrence is a relatively rare adverse outcome that occurs between 1% and 9% of patients treated by PN [3,4], although this percentage is likely to increase slightly in the next few years as a consequence of the rising spread of PN indication also for larger RCCs [5].

In this context, the role of redo PN for recurrent RCC is still overlooked. Only few studies explored the effects of either PN or radical nephrectomy (RN) on survival outcomes after previous local therapy for RCC [6–9]. As such, it is still controversial whether PN may represent a safe and effective treatment option as compared with RN also in the redo renal surgery setting. One might argue that PN may expose the patients to a non-negligible risk of undermining cancer control. Moreover, the risk for increased perioperative complications might be equally disturbing.

To provide an answer to these clinical unmet needs, we sought to design this prospective clinical study, aiming to evaluate the feasibility, safety, and oncologic outcomes of salvage PN for local recurrence after previous nephron-sparing surgery (NSS). As general PN surgical concepts cannot be translated automatically to the redo surgery scenario, we decided to additionally focus on the surgical tricks commonly employed at our institution during robot-assisted PN in this specific subgroup of patients.

2. Patients and methods

2.1. Patients and dataset

After obtaining the local ethical committee approval, we prospectively gathered data from patients treated with robotic redo PN for locally recurrent RCC after previous NSS from January 2017 to January 2023. Local recurrence was defined as any recurrence in the ipsilateral retroperitoneum, indicating the exact anatomical location of recurrence (whether distant or not from the tumor resection bed). Preoperative features of patients including age, gender, body mass index, and comorbidity status, assessed by the Charlson Comorbidity Index, the Eastern Cooperative Oncology Group performance status score, and the American Society of Anesthesiologists physical status classification system, were collected. Patients with distant metastases were excluded. All patients were scored according to the Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) [10] and RENAL nephrometric systems [11]. Operative time, warm ischemia time, and intra- and postoperative complications were recorded. Intraoperative complications were defined as all the events occurring between the induction of the anesthesia and patient awakening that could potentially cause injury and require unplanned surgical maneuvers. Postoperative complications were defined as any event occurring until the 90th postoperative day, altering the normal postoperative course and/or delaying discharge. The severity of postoperative complications was graded according to the Clavien-Dindo classification system [12]. Tumor stage was classified according to the 2017 TNM criteria [13] and nucleolar grading according to the most recent International Society of Urological Pathology grading recommendation [14]. Histopathology was reviewed according to the World Health Organization 2016 classification. The presence of ink at the resected margins on gross assessment, confirmed by microscopic extension of malignant cells at the stained margins on the final histopathologic examination, was reported as a positive surgical margin (PSM). The width of the tissue from the healthy renal parenchyma to the tumor was assessed in the macroscopically thicker score–specific areas of the surface, intermediate, and base pathologic specimens. Thus, the type of surgical resection technique was prospectively assigned to the pathologic specimen in the operating theater according to the surface-intermediate-base (SIB) score [15]. In particular, the resection technique was classified visually by the surgeon as enucleation (SIB score 0–1), hybrid enucleation (SIB score 2), enucleoresection (SIB score 3–4), or resection (SIB score 5) according to the SIB score.

The follow-up schedule included blood analysis, chest x-ray, and ultrasonography of the abdomen followed by the alternating use of a computed tomography scan performed every 6 mo from the 1st to the 5th postoperative year and then annually according to the risk profile, as postulated by the European Association of Urology guidelines [1].

2.2. Surgical technique

A detailed illustration of the robotic surgical steps employed at our institution for redo PN can be found in the accompanying video material. For the present series, the Si Da Vinci robotic platform was used in all cases (Intuitive Surgical, Sunnyvale, CA, USA). A 30° and a 0° laparoscope were preferred in case of a transperitoneal and a retroperitoneal approach, respectively. A three-arm configuration was chosen in all cases treated by a retroperitoneal approach, while a four-arm configuration was occasionally employed for the transperitoneal approach, depending on tumor location and complexity.

The surgical technique employed at our institution for robotic PN has already been described extensively [16,17]. In brief, once the tumor template has been marked with monopolar cautery, the natural, relatively avascular anatomic dissection plane is developed by blunt dissection using circumferential, dynamic tractions with the two robotic arms that lift the tumor off the parenchymal bed. As such, the intent is to preserve as much vascularized renal tissue as possible by avoiding the removal of macroscopic healthy renal tissue. Nevertheless, classic PN concepts may meaningfully vary when dealing with a locally recurrent RCC. First, redo PN may be more challenging in terms of hilar dissection due to a potential peripheral tissue reaction ultimately leading to scar tissue formation and fibrosis secondary to previous surgery performed. As such, whenever technically feasible, clampless PN without vascular pedicle isolation was performed considering the dimension of the tumor, its site, and the exophytic rate.

Second, tumor isolation may also be quite difficult depending on the grade of fibrosis and the extent of previous renal isolation. In this regard, the use of intraoperative ultrasonography is gaining attention as a crucial tool to approach complex cases safely and effectively. In particular, the possibility to use intraoperative ultrasound in robotic surgery, rather than the direct vision, allows better defining the tumor margins, even if renal capsule is not completely fat free, thus avoiding unanticipated kidney decapsulation when approaching peritumoral fat. Additionally, intraoperative ultrasound meaningfully helps the surgeon in directly individuating and managing the renal mass, in order to limit perinephric fat dissection in those cases with adherent perinephric fat or extensive adherences.

Third, following an enucleative dissection plane is always the preferred resection strategy, although in some redo PN it may be arduous since the natural cleavage plane has been twisted by previous surgery (especially for the local recurrences on tumor resection bed). In such cases, a hybrid enucleative-enucleoresective dissection strategy may be chosen to balance oncologic and functional outcomes, contemporarily maximizing the volume of vascularized renal parenchyma.

2.3. *Statistical analysis*

For statistical purposes, independent variables included all patient- and tumor-related data. Descriptive statistics were obtained reporting medians (and interquartile ranges [IQRs]) for continuous variables, and frequencies and proportions for categorical variables, as appropriate. Statistical analyses were performed using SPSS v. 27 (IBM SPSS Statistics for Mac; IBM Corp, Armonk, NY, USA). All tests were two sided, with a significance set at $p < 0.05$.

3. Results

Overall, 26 patients were considered eligible for the present study. Table 1 shows baseline clinical and demographic characteristics of the patients included in the study. Eighteen (69.2%) patients were male, and the median age was 63 (IQR 59–72) yr. The median clinical diameter was 3.5 (IQR 2.2–4.9) cm and the median PADUA score was 8 (IQR 7–9). In two (7.7%) cases, patients presented with a bilateral renal tumor. One (3.8%) functional and six (23.1%) surgical single kidney patients were recorded. All patients had been treated by previous PN, being laparoscopic and robotic in four (15.4%) and 22 (84.6%) patients, respectively. The median time from previous NSS to local recurrence was 38 (IQR 13.8–97) mo. In 14 (53.8%) cases, the recurrence was found at the level of previous tumor resection bed, and four (15%) patients had a PSM reported at the time of primary tumor resection.

Table 1 – Preoperative features of patients treated with robotic redo partial nephrectomy for local recurrence after previous nephron-sparing surgery

Gender, no. (%)	Male	18 (69.2)
	Female	8 (30.8)
Age, median (IQR)		63 (59–72)
BMI, median (IQR)		25.20 (21.35–28.48)
Charlson Comorbidity Index, no. (%)	1	2 (7.7)
	2	11 (42.3)
	3	12 (46.2)
	>3	1 (3.8)
Charlson score, median (IQR)		2 (2–3)
Tumor side, no. (%)	Right	11 (42.3)
	Left	13 (50)
	Bilateral	2 (7.7)
Clinical diameter (cm), median (IQR)		3.5 (2.2–4.9)
Clinical T stage, no. (%)	cT1a	14 (53.8)
	cT1b	6 (23.1)
	cT2a	3 (11.5)
	cT3a	3 (11.5)
PADUA score, median (IQR)		8 (7–9)
PADUA score complexity, no. (%)	6–7 (low)	9 (34.6)
(PADUA score)	8–9 (medium)	12 (46.2)
	≥10 (high)	5 (19.2)
Preoperative creatinine serum level (mg/dl), median (IQR)		1.06 (0.85–1.18)
Preoperative eGFR (ml/min/1.73 m^2), median (IQR)		72.1 (51.6–90.6)
Single kidney, no. (%)	No	19 (73.1)
	Functional	1 (3.8)
	Surgical	6 (23.1)
Time to recurrence (mo), median (IQR)		38 (13.8–97.0)
Positive surgical margins at the time of primary tumor resection, no. (%)		4 (15.4)
Recurrence site, no. (%)	Previous tumor resection bed	14 (53.8)
	Elsewhere in the ipsilateral kidney	12 (46.2)

BMI = body mass index; eGFR = estimated glomerular filtration rate; IQR = interquartile range; PADUA = Preoperative Aspects and Dimensions Used for an Anatomical.

Intraoperative features are reported in Table 2. The median operative time was 177 (IQR 148–200) min, and hilar clamping was performed in 14 (53.8%) cases with a median warm ischemia time of 16 (14.5–22) min. Intraoperative complications were recorded in two (7.7%) cases: one pancreatic and one vascular pedicle injury. No conversions to RN occurred. The median SIB score was 2 (IQR 1–2). In particular, pure enucleation (SIB score 0–1), hybrid enucleation (SIB score 2), and pure enucleoresection (SIB score 3) were recorded in 13 (50%), eight (30.8%), and five (19.2%) cases, respectively.

Postoperative and pathologic features are summarized in Table 3. The median length of hospitalization was 5 (IQR 4–6) d; pT1a, pT1b, pT2, and pT3a disease were recorded in 18 (69.2%), five (19.2%), one (3.8%), and two (7.7%) cases, respectively. Two (7.7%) patients experienced perioperative anemia requiring blood transfusion. No major (Clavien-Dindo ≥3) complications occurred. The most common tumor histotype was clear cell RCC, being recorded in 61.5% of patients. PSMs were registered in three (11.5%)

Table 2 – Intraoperative features of patients treated with robotic redo partial nephrectomy for local recurrence after previous nephron-sparing surgery

Hilar clamping, no. (%)	Performed		14 (53.8)
	Not preformed		12 (46.2)
Warm ischemia time (min), median (IQR)			16 (14.5–22)
Operative time (min), median (IQR)			177 (148–200)
Estimated blood loss, median (IQR)			260 (125–450)
Intraoperative complications, no. (%)			2 (7.7)
SIB score, median (IQR)			2 (1–2)
SIB score, no. (%)	0		3 (11.5)
	1		10 (38.5)
	2		8 (30.8)
	3		5 (19.2)
Resection technique according to site of local recurrence, no. (%)	Previous tumor resection bed (overall 14 patients)	SIB score 0	1 (7.1)
		SIB score 1	0 (0.0)
		SIB score 2	8 (57.1)
		SIB score 3	5 (35.8)
	Elsewhere in the ipsilateral kidney (overall 12 patients)	SIB score 0	2 (16.7)
		SIB score 1	10 (83.3)

IQR = interquartile range; SIB score = surface-intermediate-base score.

Table 3 – Postoperative features of patients treated with robotic redo partial nephrectomy for local recurrence after previous nephron-sparing surgery

Postoperative creatinine serum level (mg/dl), median (IQR)		1.29 (0.90–1.82)
Postoperative eGFR (ml/min/1.73 m^2), median (IQR)		55 (33.0–72.3)
3 POD – preoperative Δ creatinine serum level (mg/dl), median (IQR)		0.10 (–0.01; 0.45)
6 mo – preoperative Δ creatinine serum level (mg/dl), median (IQR)		0.13 (–0.12; 0.90)
12 mo – preoperative Δ creatinine serum level (mg/dl), median (IQR)		0.07 (–0.16; 1.02)
Last follow-up – preoperative Δ creatinine serum level (mg/dl), median (IQR)		–0.13 (0.08; –0.45)
Length of hospitalization (d), median (IQR)		5 (4–6)
Surgical complications, no. (%)	Clavien-Dindo ≤2	2 (7.7)
	Clavien-Dindo ≥3	0 (0)
RCC histotype, no. (%)	Clear cell	16 (61.5)
		1. NG 2 (5)
		2. NG 3 (10)
		3. NG 4 (1)
	Papillary	7 (27)
		1. NG 2 (3)
		2. NG 3 (4)
	Chromophobe	1 (3.8)
	Other	2 (7.7)
		1. NG 3 (2)
pT stage, no. (%)	pT1a	18 (69.2)
	pT1b	5 (19.2)
	pT2a	1(3.8)
	pT3a	2 (7.7)
pN stage, no. (%)	pNx	20(76.9)
	pN0	4 (15.4)
	pN1	2 (7.7)
Surgical margins status, no. (%)	Positive	3 (11.5)
	Negative	23 (88.5)
Nucleolar grade, no. (%)	2	8 (30.8)
	3	16 (61.6)
	4	1 (3.8)
	NA	1 (3.8)
Concordance between histology of primary and relapsing tumor, no. (%)		24 (92.3)
Local recurrence, no. (%)	Yes	3 (11.5)
	No	23 (88.5)
Disease progression, no. (%)	Yes (lungs)	2 (7.7)
	No	24 (92.3)
Survival status, no. (%)	Alive	24 (92.3)
	Cancer-related death	1 (3.8)
	Non–cancer-related death	1 (3.8)
Follow-up length (mo), median (IQR)		37 (16–45)

eGFR = estimated glomerular filtration rate; IQR = interquartile range; NA = not assigned; NG = nucleolar grade; POD = postoperative day; RCC = renal cell carcinoma.

cases. The histology of primary and relapsing tumor was concordant in 24 (92.3%) patients. At a median follow-up of 37 (IQR 16–45) mo, five (19%) patients experienced disease recurrence, being local and systemic in three (11.5%) and two (7.7%) patients, respectively. Only one (3.8%) cancer-related death was recorded. An insight into the surgical and pathologic features of those patients experiencing further local or systemic recurrence after redo PN is provided in Supplementary Table 1. No statistically significant differences were recorded in terms of Δ(postoperative – preoperative) creatinine serum level of patients treated with robotic redo PN stratified for resection technique (SIB score 0–1 vs SIB score ≥2) at 3rd postoperative day, 6- and 12-mo, and last follow-up evaluation (Supplementary Table 2).

4. Discussion

Rising enthusiasm for NSS has progressively led to the expansion of PN indication to highly complex and cT2 renal tumors, demonstrating favorable functional and oncologic outcomes in experienced centers [18,19]. On the contrary, such an attitude may unequivocally result in a higher risk for PSMs, tumor upstaging, and a risk for tumor recurrence after NSS, as a direct consequence of the increasing complexity of renal tumors potentially amenable to PN [20,21]. In this scenario, there is a growing interest among PN surgeons to understand whether redo PN may be a feasible and safe treatment option for locally recurrent RCC. As such, to address this unmet need, in this study, we sought to analyze surgical, functional, and survival outcomes of locally recurrent RCC patients after primary NSS.

The first key finding of the study is that redo PN showed an excellent safety profile, since no conversions to RN or open surgery were recorded. Only two intraoperative complications were recorded—one pancreatic and one vascular pedicle injury. Vascular pedicle isolation may indeed result in a non-negligible challenging task, since fibrosis from previous surgery may prevent the surgeon to obtain a good exposure of the renal artery. This is particularly true for right-sided renal masses, in which it may be beneficial to dissect and isolate the renal vein also (especially if the tumor is hilar or some back bleeding from inferior vena cava may be expected). In this context, the correct evaluation of tumor nephrometry and the perception of tumor vasculature represent two main features [22]. It should be noted that in nearly 46% of cases, the surgeon decided to avoid pedicle isolation and go straight for tumor excision. This is also supported by recent evidence showing no differences in terms of safety, effectiveness, and residual renal function between the on- and off-clamp approaches [23–26]. In addition, tumor isolation itself may sometimes result in a difficult task, when previous surgery has been performed. Notably, in all cases, intraoperative ultrasonography was employed. Indeed, the possibility to use intraoperative ultrasound in robotic surgery, rather than the direct vision, allowed timely identification of the tumor margins even if the renal capsule was not completely fat free, avoiding extensive, time-consuming perinephric fat dissections. In this context, intraoperative ultrasonography may also be useful in avoiding unanticipated kidney decapsulation when approaching peritumoral fat.

The second key finding of our study is that surgical resection strategy and, in result, the resection technique employed, may significantly vary in locally recurrent RCCs, mainly on the basis of several baseline tumor-related features [27]. In this context, by harnessing the SIB score to report resection techniques performed in a standardized fashion, the current manuscript can contribute to the ongoing debate and overcomes the limits of previous studies, ultimately providing novel findings that may help better contextualize the current robotic redo PN literature. In particular, the most common resection technique employed was pure enucleation, which was recorded in half of our cohort, thus further confirming the safety and high penetrance of such PN attitude. Indeed, the rationale for tumor enucleation can be ascribed to the distinct anatomical characteristics of the tumor-parenchyma interface, which allows for the definition of a constant anatomic dissection plane for tumor excision [28]. By developing the anatomic cleavage plane following tumor pseudocapsule, it is already well established how robotic tumor enucleation might also allow surgeons to widen the indications for PN in case of challenging, highly complex renal masses, especially if these are not perfectly round shaped or in close contact with the urinary collecting system [20,29]. However, such concepts cannot automatically be translated to locally recurrent RCCs on previous tumor resection bed. Indeed, in this case, it may be arduous to identify the correct tumor-parenchyma interface, which might have been altered by previous surgery due to fibrosis or presence of clips or hem-o-loks. Notably, in our series, we found higher adoption of hybrid enucleation or enucleoresection in case of tumor recurrence on previous tumor resection bed. Indeed, in such cases, the surgeon is able to carefully and wisely adapt the primary resection strategy and, in turn, the resection technique employed [30]. In particular, the surgeon generally started with an "enucleoresective strategy" leaving a margin of healthy renal parenchyma surrounding the tumor. Nevertheless, whenever possible, he/she "coned down" to the tumor base and, afterward, enucleated the deepest portion of the mass away from the kidney, thus maximizing the percentage of healthy renal parenchyma left intact after redo PN. Avoiding pedicle clamping and adopting a pure/hybrid enucleation strategy in most cases allowed safe excision of all recurrent RCCs in our series, contemporarily optimizing functional results, as demonstrated by a nonsignificant change in kidney function after surgery irrespective of the resection technique employed.

Finally, the current paper may add a further little cornerstone toward an in-depth knowledge of ipsilateral renal recurrence biology. Only four (15%) patients had a PSM reported at the time of primary tumor resection, thus relatively minimizing the impact of surgical margin status [31]. On the basis of such premises, Antonelli and coworkers [32] tried to classify ipsilateral RCC recurrence into three different subtypes, depending on the characteristics of the tumor-parenchyma interface and the resection bed (type A attributable to an incomplete resection during primary PN, type B associated with microvascular embolization, and type C showing a distinct neoplastic focus in the context of "true" multifocality). Our data seem to be relatively consistent, hence suggesting that other competing adverse features may act in determining local recurrence apart from an incomplete primary tumor excision. Indeed, nearly 46% of our patients showed RCC recurrence far from the tumor resection bed, thus ascribing tumor relapse more likely to a newborn RCC or true multifocality, rather than to tumor persistence. Unfortunately, the low number of patients prevented us from drawing further conclusions.

Despite its strengths, few limitations of the study should be highlighted.

The relatively small sample size together with the limited number of events might have undermined the survival analysis and the evaluation of potential predictors of recurrence in our series. Second, all cases were performed by surgeons with extensive experience in robotic PN, as such our conclusions might not be directly applicable to all surgeon- or center-related contexts. Third, the learning curve of the surgeons was not considered in the present study.

Acknowledging these limitations, our findings provide further evidence to assess the feasibility, reproducibility, and safety of redo PN for the treatment of locally recurrent RCCs after NSS, either on previous tumor resection bed or elsewhere in the kidney. The employment and the assignment of the SIB score represent a major strength of the study, allowing a deep insight into surgical nuances, resection strategy, and in turn, resection technique employed case by case for redo PN in a high-volume robotic center.

5. Conclusions

Our study highlights the feasibility and safety of redo PN for the treatment of locally recurrent RCCs after NSS, either on previous tumor resection bed or elsewhere in the kidney. A proper evaluation of the site of recurrence, tumor nephrometry, and perception of its vasculature represents key features in order to tailor pedicle management and tumor resection technique case by case, thus maximizing both local cancer control and functional outcomes.

***Author contributions*:** Fabrizio Di Maida 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: Di Maida, Grosso, Minervini.
Acquisition of data: Lambertini, Salamone, Paganelli, Cadenar, Gallo, Coco.
Analysis and interpretation of data: Di Maida, Grosso.
Drafting of the manuscript: Di Maida.
Critical revision of the manuscript for important intellectual content: Masieri, Minervini, Tuccio.
Statistical analysis: Di Maida, Grosso, Campi.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2023.09.007.

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