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Review

Current strategies to diagnose and manage positive surgical margins and local recurrence after partial nephrectomy

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Robot-assisted partial nephrectomy

Abstract *Objective:* No standard strategy for diagnosis and management of positive surgical margin (PSM) and local recurrence after partial nephrectomy (PN) are reported in literature. This review aims to provide an overview of the current strategies and further perspectives on this patient setting.
Methods: A non-systematic review of the literature was completed. The research included the most updated articles (about the last 10 years).
Results: Techniques for diagnosing PSMs during PN include intraoperative frozen section, imprinting cytology, and other specific tools. No clear evidence is reported about these methods. Regarding PSM management, active surveillance with a combination of imaging and laboratory evaluation is the first option line followed by surgery. Regarding local recurrence management, surgery is the primary curative approach when possible but it may be technically difficult due to anatomy resultant from previous PN. In this scenario, thermal ablation (TA) may have the potential to circumvent these limitations representing a less invasive alternative. Salvage surgery represents a valid option; six studies analyzed the outcomes of nephrectomy on local recurrence after PN with three of these focused on robotic approach. Overall, complication rates of salvage surgery are higher compared to TA but ablation presents a higher recurrence rate up to 25% of cases that can often be managed with repeat ablation.
Conclusion: Controversy still exists surrounding the best strategy for management and diagnosis of patients with PSMs or local recurrence after PN. Active surveillance is likely to be the optimal first-line management option for most patients with PSMs. Ablation and salvage surgery both represent valid options in patients with local recurrence after PN. Conversely, salvage PN and radical nephrectomy have fewer recurrences but are associated with a higher complication rate compared to TA. In this scenario, robotic surgery plays an important role in improving salvage PN and radical nephrectomy outcomes.

1. Introduction

To date, partial nephrectomy (PN) represents the standard of care for clinically T1 ($\leq$7 cm) and T2 ($>$7 cm) renal tumors when technically feasible [1,2]. PN contributes to renal function preservation and possibly reduces other-cause mortality without compromising oncological outcomes [3]. The primary goal of nephron-sparing surgery (NSS) is to remove the tumor with the aim of negative surgical margins (NSMs) [3]. However, the possibility of residual tumor in the kidney bed represents one of the challenges in performing PN [3].

According to the current literature, the prevalence of positive surgical margin (PSM) after NSS varies according to the practice setting, tumor characteristics, and type of surgery [4]. However, there is no clear consensus regarding the negative impact of PSM on local recurrence, distant metastasis, or long-term oncological outcomes, as well as intraoperative diagnosis or postoperative management [5–8].

Different from PSM, local recurrence (or local relapse) represents a significant clinical challenge as is often accompanied by poor prognosis [9]. However, even in this scenario, recommendations are difficult to generalize for the varying and complex appearance of local recurrence in the kidney after PN [9].

The aim of this review is to provide an overview of the current strategies to diagnose and manage PSMs and local recurrence after PN.

2. Methods

A non-systematic review of the literature within the PubMed (Medline), and Ovid database was completed using the keywords "partial nephrectomy", "nephron-sparing surgery", "positive margin", and "local recurrence" or "local relapse" filtered for human and adult pathologic conditions. The research included the most updated articles (about the last 10 years) published in core clinical journals in English (up to December 2021). The peer-review process was performed by two authors (Gentile C and Torre G) and supervised by a senior author (Carbonara U). After a first screening based on title and abstract, full texts of potentially eligible studies were evaluated and selected. The reviewers independently carried out data extraction collecting the main study's features, including first author, year of publication, country, number of patients included in the analysis, main pathological characteristics of patients included, primary outcomes, and main findings.

Results are reported as a narrative review with one primary aim, namely to evaluate the current strategy for diagnosis and management of PSMs after PN. The secondary aim of this review was to provide an overview of the diagnosis and management of the local recurrence after PN. Because of the absence of randomized clinical trials and the low prevalence of PSMs, weighted cumulative and comparative analysis were not performed.

3. Results

The main characteristics of studies included in this review are reported in Tables 1–3. The narrative review includes four areas of interest which are discussed below.

4. Techniques to diagnose and minimize the risk of PSM after PN

In the following section, different techniques for diagnosing and minimizing the risk of PSMs during PN will be discussed including the intraoperative frozen section (FS), imprinting cytology (IC) assessment, ultrasound (US), as well as other specific tools (Table 1).

4.1. Intraoperative FS assessment during PN

Overall, FS technique is typically performed when there is a concern for incomplete tumor resection at the time of surgery. FS helps in clinical decision-making in whether additional tissue excision or possible conversion to radical nephrectomy (RN) is necessary if appropriate tumor control cannot be achieved through NSS [10]. However, several studies have assessed the routine utility of FS during PN leading to conflicting conclusions [10–12].

Venigalla et al. [10] evaluated the impact of FS on final pathological PSM and patient outcomes. Overall, 433 patients undergoing PN (447 renal masses; 136 open and 311 laparoscopic PN) were analyzed. Of these, 293 (67.7%) patients underwent 300 (67.1%) PNs with FS assessments. The authors found that PSMs were presented significantly more often in patients undergoing PN without FS (17.7% *vs.* 4.3%, $p<0.001$). Stratifying for histological subtype, the authors showed that FS assessment did not considerably contribute to preventing recurrence in the subgroup of renal cell carcinoma (RCC) cases, even if performing FS during laparoscopic PN strongly correlated with improved recurrence-free survival in patients with pT1 ($p=0.004$) or exophytic ($p=0.011$) RCC. No impact of FS assessment on recurrence rate was seen in any subgroup of patients undergoing open PN (OPN). The authors concluded that FS leads to significantly fewer PSMs than no FS assessment. However, there may be a role for FS in selected groups of patients who have presumed stage T1 or exophytic RCC and who will undergo laparoscopic resection.

The value of FS analysis can be questioned as important discrepancies between the FS assessments and final pathologies were reported in several papers [11,12]. In a retrospective fashion, Gordetsky et al. [11] observed a relatively high false-negative rate and inconsistency in influencing intraoperative management of resection beds which are all arguments against the routine use of FS. From a technical point of view, FSs were obtained by intraoperative biopsy of the nephrectomy bed. In selected cases, the renal mass was sent for FS too for determining the type of tumor. Diagnoses were classified as positive, negative, or atypia (defined as changes suspicious for, but not diagnostic of, carcinoma) [11]. In this paper, 576 intraoperative FSs were performed in 351 cases to assess the PN tumor bed margin, 19 (5.4%) of which also had a mass sent for FS to assess the tumor type. In terms of predicting the final specimen margin, 17 of 333 (5.1%) cases that were negative on the FS of resection bed and kidney reported a final PSM [11]. According to the authors, the intraoperative management was influenced in six of nine cases with a positive FS diagnosis and one of nine cases with an FS diagnosis of atypia. Similarly, Hillyer et al. [12] reported a comparable PSM rate between 128 and 214 patients who underwent robot-assisted PN (RAPN) with and without FS assessment. The positive FS assessment changed the intraoperative management of three patients who underwent radical nephrectomy, further resection of surgical bed, and observation only. Final pathology results demonstrated seven cases of PSM, 1 (1%) in the FS group and 6 (3%) in the no-FS group ($p=0.19$).

Sidana et al. [13] evaluated the preferences and practice patterns of urologists regarding intraoperative FS during PN through a 17-item questionnaire that was sent to the members of the Society of Urologic Oncology and Endourological Society. A total of 197 responses were received. Overall, 69% and 58% of respondents chose to obtain FS (always or sometimes) during OPN and laparoscopic PN, respectively. Younger surgeons were reported less likely to obtain FS during OPN. The main reasons for avoiding the use of FS during PN were "confidence about complete resection" (79%), and the opinion that FSs do "no change in management with positive margins" (35%) [13]. To note, 95% of the respondents would not recommend additional treatment for positive margins on final pathology as PSM after resection does not mean that there will be evidence of residual tumor on kidney bed [13]. According to the authors, urologists should be aware of the limitations of FS analysis before embarking on a wider resection or a RN that can lead to unnecessary kidney damage and increased surgical morbidity for positive FS [14]. Additional tools are needed to better assess the quality of the resection during PN. Overall, the quality of evidence is poor and fragmented.

4.2. Cytology assessment during PN

Intraoperative IC examinations have been used effectively to assess surgical margin positivity in other entities such as breast, brain, and oropharyngeal tumors [15].

In a prospective study, Özsoy et al. [15] evaluated the intraoperative IC and FS examinations in 114 tumors from 105 consecutive patients who were treated with enucleation PN. Overall, FS and IC groups were compared with the final histopathological examination which could be considered the gold standard. Before performing FS, the specimen's base and resection margins were rolled over glass slides to obtain cells for IC assessment. The whole IC process is completed ranging from 60 to 80 seconds. IC revealed 21 tumors with PSM with two false positives. IC showed a specificity of 98%, a sensitivity of 100%, a positive and a negative predictive value of 90% and 100%, respectively. FS examinations revealed positive resection margins in 20 tumors with only a single false positive. Furthermore, FS examination failed to diagnose a positive resection margin in one tumor. FS examination showed specificity and sensitivity in PSM detection of 98% and 99%, as well as a

Table 1 Studies evaluating the techniques to diagnose and minimize the risk of PSMs after PN.

Study[a]	Patient/ LS, *n*	TS, cm	Pathological T2/T3, *n* (%)	Primary PN approach, %	PSM case	Other outcome
Intraoperative FS assessment						
Venigalla et al. [10], 2013	293/300[b]	—	6 (2.6)/14 (6.1)	• OPN: 39.3 • LPN: 60.7	• Lower in FS *vs.* no-FS cases (4.3% *vs.* 17.7%, $p<0.001$[d])	• FS did not contribute to preventing recurrence ($p=0.114$) • No impact of FS on recurrence. • FS during LPN correlated with improved RFS in patients with pT1 ($p=0.004$[d]) or exophytic ($p=0.011$[d]) RCC.
Hillyer et al. [12], 2013	128/—[b]	3.1	—	• All RAPN	• Similar in FS *vs.* no-FS cases (1% *vs.* 3%, $p=0.19$).	• Intra-operative management was influenced in 3 (2.3%) positive FS cases; one patient underwent radical nephrectomy, one reresection, and one observation only. • Final pathology demonstrated seven cases of PSM; 1 (1%) in FS group and 6 (3%) in the no-FS group ($p=0.19$). • OT was longer in the no-FS cohort (180 min *vs.* 193 min, $p=0.04$[d]).
Gordetsky et al. [11], 2015	351/576[b]	2.9	3 (1.1)/15 (5.4)	• OPN: 20.5 • LPN: 2.3 • RAPN: 77.2	• Similar in FS *vs.* no-FS cases (8.6% *vs.* 5.7%, $p=0.13$).	• High false-negative rate (5.1%) in FS cases ($p<0.05$[d]) • Intra-operative management was influenced in six of nine positive FS cases and in one of nine cases with diagnosis of atypia at FS.
IC assessment						
Özsoy et al. [15], 2015	105/114	—	—	• OPN: 89 • LPN: 11	• IC showed a specificity of 98%, a sensitivity of 100%, a positive predictive value of 90%, and a negative predictive value of 100% compared with histologic examination.	• Of the 21 positive resection margins, two were false positives. • Equivalent diagnostic value compared with FS analysis
Palermo et al. [16], 2013	73/83	—	—	• OPN: 90.3 • LPN: 9.7	• IC showed a specificity of 95.9%, a sensitivity of 87.5%, a positive predictive value of 70%, and a negative	• After PN, PSMs were positive in 8 of 82 (9.8%); IC reported PSM in 10 of 82 (12.2%). • Good level of agreement between intraoperative IC and final

(*continued on next page*)

Table 1 (*continued*)

Study[a]	Patient/ LS, *n*	TS, cm	Pathological T2/T3, *n* (%)	Primary PN approach, %	PSM case	Other outcome
					predictive value of 98.6% compared with histologic examination.	histologic examination (kappa value=0.751; $p<0.0001$)
Intraoperative US assessment						
Alharbi et al. [17], 2016	147/177	3.5	8 (4.5)/2 (2.3)	• OPN: 81.4 • LPN: 11.3 • RAPN: 7.3	• Four patients with PSM at US intraoperative control; only one at final histologic examination.	• The intraoperative US determined margin status with a specificity of 75%, a sensitivity of 99%, a positive predictive value of 99%, and a negative predictive value of 75% compared with histologic examination. • In only one case, the US control was not possible because no capsule was visible, and the surgical margins were negative.
Sorokin et al. [18], 2015	45/54	2.7	−/1 (0.54)	• All RAPN	• Lower in US-technique group compared with those without US-control (2% *vs.* 28%, $p=0.001$[d])	• A single patient with a PSM experienced a systemic disease recurrence.
Surface-intermediate-base margin score[c]						
Minervini [20], 2020	507/−	3.0	15 (3)/−	• EPN: 52 • ERPN: 30 • RPN: 18	• ERPN was associated with a significantly higher risk of PSM compared to EPN (OR: 2.42, $p=0.03$[d]) and RPN (OR: 5.73, $p=0.024$[d]).	• The trifecta (defined as negative surgical margins, no major perioperative surgical complications, and no postoperative acute renal impairment) rate after ERPN was significantly lower than after EPN and RPN (54.7% *vs.* 69.8% *vs.* 69.2%).

LS, lesions; TS, tumor size; PSM, positive surgical margin; PN, partial nephrectomy; FS, frozen section; IC, imprint cytology; US, ultrasound; OPN, open PN; LPN, laparoscopic PN; RAPN, robot-assisted PN; RFS, recurrence-free survival; EPN, enucleation PN; RPN, resection PN; ERPN, enucleoresection PN; RCC, renal cell carcinoma, OT, operative time; OR, odd ratio; −, not reported.

[a] All selected studies are retrospective, except Özsoy et al. [15] that is a prospective study.

[b] Patients underwent FS assessment.

[c] Surface-intermediate-base (SIB) margin score classifies the PN technique as enucleation (SIB score 0–2), enucleoresection (SIB score 3 or 4), or resection (SIB score 5) according to visual analysis of the specimen by the surgeon in the operating room after the procedure.

[d] There was a statistically significant difference.

positive and negative predictive value of 95% and 98%, respectively. The authors concluded that IC examinations exhibit equivalent diagnostic value compared with FS analysis with overall time-sparing [15]. Another study reported similar results [16]. According to the authors, one of the main advantages of IC is its ability to assess the entire tumor surface rather than a specific area [16]. Finally, IC represents an inexpensive method with the ability to give rapid and highly accurate information but with an inter-observer variability [16]. Further investigations are necessary to better address these promising results.

4.3. Intraoperative US assessment during PN

Alharbi et al. [17] evaluated intraoperative US technique in a cohort of 147 patients (177 renal masses) undergoing open, laparoscopic, and robotic PN. Before mass removal, the operator conducted intraoperative tumor localization with a high-frequency open or laparoscopic US probe. After tumor resection and immediately before performing hemostasis, US control of the surgical margins was performed. In the open surgery, the specimen was immersed in a saline solution, and the sequential US was performed to evaluate in three dimensions if the tumor's capsule was intact. In the laparoscopic approaches, the specimen was placed into a laparoscopic endo-bag filled with enough saline solution to cover the specimen, and the probe was then placed into the endo-bag. If margins were negative, hemostasis was performed. Otherwise, an extra rim of renal parenchyma was removed circumferentially to include the entire remaining margin. In only one case, the US control was not possible because no capsule was visible. US control of surgical margins of the specimens was positive in four patients. At pathology, the final results showed only one patient of four with PSM. The intraoperative US showed a specificity of 75%, a sensitivity of 99%, a positive and a negative predictive value of 99% and 75%, respectively [17]. These results seemed to be inferior to FS and IC assessment, but the heterogeneity of study cohorts and retrospective fashion of the selected study prevent any comparisons [17]. In a comparative study, Sorokin et al. [18] analyzed the outcomes of patients who underwent RARP with or without the intraoperative US assessment. Surgical margin positivity was found in 1 of 45 (2%) samples of patients who underwent US assessment during RAPN. This rate is lower ($p=0.001$) compared to the non-US group (PSMs reported in 19 of 67 masses [28%]). On multivariate analysis, technique modification with intraoperative US (odd ratio [OR] 0.04, $p=0.003$) and larger tumor size (OR 0.41, $p=0.01$) were significant predictors of a lower rate of PSM. The authors concluded that in their experience, US assessment during RAPN resulted in a dramatic improvement on PSM assessment but further evidence is required before introducing this tool in current routine clinical practice.

4.4. Surface-intermediate-base (SIB) margin score

Historically, a distance of 1 cm has been described as the appropriate "safety" margin for standard PN [5]. During the past decade, the definition of the safe margin of healthy renal tissue that should be excised with the tumor and therefore of the oncologically safest resection technique during PN became a matter of debate [19]. In this scenario, there is the need of defining the appropriate margin parameters to minimize the risk of cancer regrowth [19]. To date, no formal guidelines have been provided regarding the appropriate resection technique to optimize cancer control and renal functional preservation after surgery. A recent systematic review reported that the simple enucleation during PN (performed along with the tumor pseudo capsule, without safety margin) is at least non-inferior to the standard PN resection technique for clinical T1 and T2 renal tumors concerning PSM and local recurrence rate after a minimum follow-up of 24 months [19].

In a prospective fashion, Minervini et al. [20] evaluated the pattern of resection techniques during PN in 507 patients, evaluating the SIB margin score and classifying the PN technique as enucleation (SIB score 0–2), enucleoresection (SIB score 3 or 4), or resection (SIB score 5) according to visual analysis of the specimen by the surgeon in the operating room after the procedure. The trifecta rate after enucleoresection (defined as NSMs, no major perioperative surgical complications, and no postoperative acute renal impairment) was significantly lower than after enucleation and resection (54.7% *vs.* 69.8% *vs.* 69.2%). Moreover, the resection technique (enucleoresection *vs.* enucleation and resection) was the only significant predictor of PSM. The enucleoresection technique was associated with a higher risk of PSMs compared to enucleation (OR: 2.42, $p=0.03$) and resection (OR: 5.73, $p=0.024$). From a technical viewpoint, the microscopic layer of a healthy parenchyma leaving during enucleation, as well as the wide parenchymal margin far beyond the tumor contours leaving during resection could be potentially protective against PSMs. This concept is particularly relevant when tumors are imperfectly spherical with resection contours that can vary unexpectantly [19].

5. Strategy to manage patients with PSMs after PN

Several studies suggested that in case of PSM after PN, it is reasonable to pursue ongoing active surveillance (AS) with a combination of imaging and laboratory evaluation [21,22]. These recommendations are based on the low risk of local and metastatic progression and the lack of consensus surrounding the oncologic potential associated with PSM [21,22]. However, other reports analyzed the outcomes of patients who underwent surgery for a PSM with controversial results [23,24] (Table 2).

5.1. AS and follow-up in patients with PSMs

In one of the first series on AS in the setting of PSM patients, Lopez-Costea et al. [22] showed no evidence of recurrence in nine of eleven patients with PSM (ranging from pathological T1 to pathological T3 disease) undergoing AS after OPN within a median follow-up of 80.5 months. Otherwise, two PSM patients required RN (one for postoperative bleeding and another as an elective procedure). Interestingly to note, none of the two patients with PSM undergoing surgery presented residual disease in their last pathology report. This

Table 2 Studies evaluating the impact of AS or surgical management on patients with PSMs after PN.

Study	Study type	Patient, *n*	Primary PN approach, *n* (%)	PSM case, *n* (%)	Histological subtype of primary PN, *n* (%)	F/Up, month	Other outcome
AS[a]							
Lopez-Costea et al. [22], 2010	Retrospective and single-center	137	• All OPN	11 (8.0)	• ccRCC: 3 (33.3) • pRCC: 2 (22.2) • chRCC: 2 (22.2) • hoRCC: 2 (22.2)	80.5	• Nine patients in AS (evaluated with CT every 6 months for 2 years, and then every year for 5 years, then alternating CT or ultrasound) • Two patients completed nephrectomy (one for bleeding and one as elective). • No local or metastatic disease
Raz et al. [28], 2010	Retrospective, single-center, and comparative study evaluating AS *vs.* treatment for patients with PSM	114	• All OPN	17 (14.9)	—	71	• Nine patients with PSM proceeded with completion nephrectomy (five immediate and four subsequent surgery). • Four patients underwent re-excision of the renal crater. • Tumor cell remnants in the kidney were seen in only 2 (15%) patients after completion RN or re-excision. • Four patients underwent AS. • No difference in disease progression, cancer recurrence, or cancer-specific mortality between AS and completion nephrectomy groups.
Petros et al. [29], 2018	Retrospective, single-center, and comparative study of PSM *vs.* NSM patients	2297	• OPN: 28 (82.4) • LPN: 1 (2.9) • RAPN: 5 (14.7)	34 (1.5)[b]	• ccRCC: 21 (62) • pRCC: 9 (26) • chRCC: 2 (6) • Unclassified 2 (6)	62	• All patients received AS and no adjuvant intervention. • Four patients developed local recurrence, four distant kidney recurrences, and five metastases. • PSM patients were at a higher risk of shorter overall survival (p=0.001[d]), local RFS (p=0.003[d]), distant RFS (p=0.032[d]), and metastasis-free survival (p=0.018[d]) compared to NSM. • There was association between PSM and bilateral tumors, prior treated RCC at presentation and higher nephrometry score in patients with PSM compared to those with negative surgical margins.
Shah et al. [27], 2016	Retrospective and multi-center	1240	• OPN 1095 (88.3) • MIPN: 145 (11.7)	97 (7.8)	• ccRCC: 69 (71) • pRCC: 21 (22)	33	• Recurrence developed in 69 (5.6%) patients, including 37 (3.0%) with high

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Table 2 (*continued*)

Study	Study type	Patient, *n*	Primary PN approach, *n* (%)	PSM case, *n* (%)	Histological subtype of primary PN, *n* (%)	F/Up, month	Other outcome
					• chRCC 5 (5) • Unclassified 2 (2)		risk disease (eg. pT2-pT3a or Fuhrman Grade III-IV) ($p<0.05$[d]).
Surgical management							
Carvalho et al. [24], 2020	Retrospective, single-center, and comparative study of PSM *vs*. NSM patients.	388	• OPN: 3 (18.8) • LPN: 10 (62.5) • Conversion: 3 (18.8)	16 (4.1)	• ccRCC: 7 (43.8) • pRCC: 3 (18.8) • chRCC: 6 (37.5)	Short (not specify)	• Higher surgeon experience was associated with a lower PSM incidence (2.6% if $\geq$30 PNs *vs*. 9.6% if $<$30 PNs; $p=0.02$[d]). • Secondary total nephrectomy was performed in the four selected cases (25%). • Recurrence rate were higher for PSM group *vs*. NSM group (18.7% *vs*. 4.2%, $p=0.007$[d]). • Overall survival was similar. • Multivariate analysis revealed that high-risk tumor ($p=0.05$) and low experience ($p=0.03$[d]) could predict PSM.
Bensalah et al. [14], 2010	Retrospective, multi-center, and comparative study of PSM *vs*. NSM patients	775	• OPN: 95 (85.6) • MIPN: 16 (14.4)	111 (14.3)[b]	• ccRCC: 75 (67.6) • pRCC: 29 (26.1) • chRCC: 7 (6.3)	37	• 93 (83.8%) patients were closely followed with laboratory and instrumental examinations[c]; 3 (2.7%) and 15 (13.5%) patients underwent repeated PN and RN, respectively. • After surgery, residual tumor was found in 7 (6.3%) patients. • 11 (10%) patients had recurrences. • 12 (11%) patients died, including 6 (5.4%) patients whose deaths were related to cancer progression. • Higher number of high-grade tumors in the PSM *vs*. NSM (30% of Grade 3–4 tumors *vs*. 19.4%, $p=0.02$[d]). • Recurrence rate higher in PSM than NSM (10.1% *vs*. 2.2%, $p<0.0001$[d]). • Time to recurrence was shorter in PSM than NSM (21.4 *vs*. 24.7 months, $p=0.004$[d]).

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Table 2 (*continued*)

Study	Study type	Patient, *n*	Primary PN approach, *n* (%)	PSM case, *n* (%)	Histological subtype of primary PN, *n* (%)	F/Up, month	Other outcome
							• None of the patients who had an immediate second surgery had a recurrence. • PSM has no impact on overall survival and cancer-specific survival compared to NSM.
Sundaram et al. [25], 2011	Retrospective and single-center	29	• OPN: 7 (24.1) • LPN: 12 (41.4) • RAPN: 10 (34.5)	29 (100)	—	15	• Eight patients underwent nephrectomy, of which no one presented residual cancer in the renal remnant. • 21 underwent total re-resection of the margin, of which two presented carcinomas. • Renal functional outcomes revealed a decrease in eGFR of 25 mL/min/1.73 m^2 in patients who underwent RN, and 4 mL/min/1.73 m^2 in patients who underwent re-resection of the margin with preservation of the renal unit. • Average decrease in GFR was 4 *vs*. 25 mL/min/1.73 m^2 for re-resection and completion RN, respectively.

TS, tumor size; PSM, positive surgical margin; PN, partial nephrectomy; OPN, open PN; LPN, laparoscopic PN; RAPN, robot-assisted PN; MIPN, minimally-invasive PN; RCC, renal cell carcinoma; ccRCC, clear cell RCC; pRCC, papillary RCC; chRCC, chromophobe RCC; hoRCC, hybrid oncocytic RCC; NSM, negative surgical margin; RN, radical nephrectomy; AS, active surveillance; F/Up, follow-up; RFS, recurrence-free survival; CT, computed tomography; eGFR, estimated glomerular filtration rate; —, not reported.

[a] The imaging and laboratory evaluation was used in AS.

[b] Microscopic PSM was defined as presence of ink at the resected margins on gross assessment before tumor manipulation, which was confirmed by microscopic extension of malignant cells at the stained margins on final pathology.

[c] The decision for observation versus immediate surgery was made by the surgeon according to his own practice patterns.

[d] There was a statistically significant difference.

result is in concordance with another study [25]. After an appropriate-long follow-up, there was no local recurrence or distant progression in the study group [22]. The authors concluded that according to their experience, PSMs in NSS can be managed conservatively with AS, avoiding extensive reoperation without compromising long-term oncological outcomes. These data were confirmed by an extended version by Fernández-Concha Schwalb et al. [26] reporting cancer-specific survival (CSS) and disease-free survival at 5 years of 87.5% and 93.3%, respectively.

A risk stratification based on tumor pathology and stage could be performed to establish an appropriate protocol of follow-up monitoring. Shah et al. [27] assessed the outcomes of 97 (7.8%) patients with PSM (of a cohort of 1240) dividing them into low risk and high risk. The low-risk group corresponded to pathological T1 and Fuhrman Grades 1 and 2 tumors, while the high-risk group comprised pathological T2-3a or Fuhrman Grades 3–4 tumors. Based on surgeon preference, PN was completed with tumor enucleation or sharp excision, and intraoperative biopsy of the resection bed was evaluated using FS. During the follow-up, imaging included the use of cross-sectional imaging or baseline computed tomography (CT) followed by alternating use of US and CT based on surgeon preference, and X-ray was used to screen the chest, except for pathological T3a disease, for which CT may have been obtained. Recurrence developed in 69 (5.6%) patients during a median follow-up of 33 months, including 37 (3.0%) with high-risk disease. In multivariable analysis, high PSMs were associated with an increased risk of local relapse (HR 2.08, $p=0.03$). In a stratified analysis based on pathological features, a high PSM rate was associated with a higher risk of recurrence in cases considered high risk (HR 7.48, $p<0.001$) but not low risk (HR 0.62, $p=0.647$). With these results in mind, it seems logical to think that the only presence of PSM should not be considered a definitive indication for the re-management after PN, but specific histological features should be taken into account for post-PN management. However, the chances of unknown tumor multifocality may always exist, and this variable is not always under control. For these reasons, the optimal management of PSM after PN remains uncertain, and randomized prospective analyses are needed to better direct these findings.

In a retrospective comparative study, Raz et al. [28] reported no difference in cancer recurrence rate or CSS in 4 (24%) patients with PSM who were managed with AS, compared to 13 (76%) PSM patients who underwent re-surgery. Overall, 9 (53%) patients underwent RN (five immediately and four delayed but within 3 months from NSS) and in 4 (24%) patients immediate re-excision of the renal wound bed was performed. Here, the authors were able to carry out a histologic evaluation for 13 of 17 cases reporting the presence of similar tumor cells at the remaining site in only 2 (15%) cases. No difference in disease progression, cancer recurrence, or CSS between AS and re-surgery groups was observed. The authors conclude that patients should be meticulously followed up in cases where the surgeon is highly confident of resection with NSM, and if there is a high suspicion of residual tumor at the time of surgery, re-resection of the renal wound bed is recommended. In contrast, Petros et al. [29] reported shorter overall survival ($p=0.001$), local recurrence-free survival ($p=0.003$), distant recurrence-free survival ($p=0.032$), and metastasis-free survival ($p=0.018$) among 34 patients with microscopic PSM after PN who were managed only with AS strategy and received no adjuvant intervention at follow-up of 62 months. In addition, the authors found that recurrences were more commonly linked to patients who had a higher risk for multifocal tumors and their recurrence may have resulted from new primary tumors as opposed to recurrence secondary to microscopic PSM. Only four patients with PSM recurred at the resection bed while nine patients had either distant kidney recurrences ($n=4$) as a result of new primary tumors or metastases ($n=5$) away from the resection bed [29]. Notably, the take-home message was to perform an intraoperatively complete surgical excision with NSM when feasible, rather than other postoperative management of patients with PSM [29].

5.2. Surgical treatment in patients with PSMs

PSM is believed to correlate with residual tumors in the affected kidney. However, this assumption may not be entirely correct, as only one side of the margin is seen by the pathologist. There is conflicting evidence concerning the significance of PSMs, and protection from recurrence is not ensured by NSMs [23]. On the contrary, it is conceivable that, in cases of minimal PSMs, the remaining tumor may suffer from cautery or ischemia-induced necrosis [23]. Alternatively, false-positive PSMs can be created by rupture of the tumor capsule during or after resection [24]. Many experts recommend judicious use of completion nephrectomy in the setting of PSM after NSS and support the pursuit of AS due to the low rate of progression and low cancer-specific mortality rates in this subset of patients [23].

In 2010, a retrospective study including data from 26 centers in Europe and North America assessed the impact of PSM (defined as the presence of tumoral tissue on the inked surface of the tumor on final pathology assessment) on survival outcomes of 111 patients after NSS [14]. Of these, 93 (83.8%) patients were closely monitored by laboratory and instrumental examinations, 3 (2.7%) and 15 (13.5%) patients underwent repeated PN and RN, respectively. The decision for observation versus immediate delayed surgery was made by the surgeon according to his or her practice patterns. Interestingly to note, the residual tumor was found in 7 (39%) of 18 patients who underwent a second surgery, duplicating other series findings [25,30], and underlining the fact that residual disease might not be present, even if it is reported on the pathologic exam. When the authors compared PSM and NSM patients, the presence of PSM is associated with a higher recurrence rate (10.1% *vs.* 2.2%, $p<0.0001$), but CSS and OS are equivalent even after matching the two study groups. Furthermore, in a multivariable model, the margin status was not a significant predictor of recurrence or survival. These results showed that not all PSMs lead to tumor recurrence and/or cancer progression as reported by Kang et al. [31], but if a potential increase of the recurrence risk in PSM patients is present, a long and tight follow-up is needed to make sure that the incidence of recurrence and progression remains stable over time [14,31]. Carvalho et al. [24] retrospectively evaluated the risk factors for PSMs and their impact on the overall survival of 388 patients who underwent PN. In a setting of 16 (4.1%) patients with PSM, higher surgeon experience was associated with a lower PSM incidence (2.6% of cases with PSMs if more than 30 PNs were performed by surgeon *vs.* 9.6% if less than 30 PNs were performed; $p=0.02$), while higher-risk tumors ($p=0.03$) and larger pathological size ($p=0.05$) were associated with an increase in PSM rate [24]. The overall recurrence rate ($p=0.007$), local relapse rate ($p=0.02$), as well as metastasis development ($p=0.001$), and need for total ipsilateral nephrectomy ($p<0.001$) were higher in the PSM group compared to the NSM group. These results showed the heterogeneity of this topic and the need for high-quality studies that help the surgeon in the decision-making about PSM patients.

6. Techniques to diagnose and minimize the risk of local recurrence after PN

Local recurrence after PN is defined as relapse within the renal fossa or at the resection margin [32]. It may be due to an incomplete resection, multifocal disease (more typical of papillary subtype RCC or hereditary RCC syndrome) that is already present at the time of surgery, or a *de novo* metachronous neoformation [32]. The effect of PSM on recurrence after PN has remained a controversial topic [32]. In a multicenter fashion, PSMs were associated with an increased risk of relapse (HR 2.08, $p=0.03$), especially for patients presenting adverse pathological features (HR 7.48, $p<0.001$), such as sarcomatoid or rhabdoid differentiation [33]. Contrarily, other studies reported that PSM would not have an increased incidence of disease recurrence or metastasis [31].

Bertolo et al. [32] re-evaluated the pathology specimens in patients who experienced a clinical recurrence after open and robotic PN with the aim of re-define the mean of local recurrence. After reviewing a large data set of 1994 patients, 30 (1.5%) cases were diagnosed with recurrent disease at a follow-up of 39 months, which is in line with the available literature [2,34]. The authors defined local relapse as a new contrast-enhancing lesion found within or abutting the surgical resection bed of patients undergoing PN for the ipsilateral kidney, and reclassified them as "true" local recurrence if pathologists confirmed RCC (of the same subtype as the original) involving the resection bed or with the adjacent soft tissues, "new occurrence" if there was well-delineated RCC unrelated to the previous resection bed and/or of a different RCC subtype, and "micrometastatic" RCC for other subtypes. After reviewing PN and recurrence specimens, 60% of patients presented a reclassification of the disease status, and only nine patients were "truly" developed a local recurrence (with or without metastasis) of the previously resected RCC, with a single PSM case after PN. Moreover, five of nine had either sarcomatoid or rhabdoid dedifferentiation. Twelve patients were diagnosed with a new occurrence of RCC and nine patients were diagnosed with micrometastatic RCC. To note, the highest percentage of PSMs was found in the group of patients who had micrometastatic RCC (four of nine cases). Moreover, 88 of 1944 patients in the analyzed data set had PSMs but did not experience any cancer-related event within the period considered. Regarding oncological outcomes, patients with "new occurrence" RCC had higher 5-year CSS compared with patients relocated in other groups ($p=0.02$).

In contrast, Antonelli et al. [35] published an analysis of the features of 18 ipsilateral relapses of salvage PN and found three types of relapse related to different etiology, histology, and prognosis. In 12 cases, the ipsilateral recurrence harbored into the site of PN. In the remaining six cases, after microscopy of the salvage resection, the authors found only fibrosis. The authors concluded that the ipsilateral recurrence is more frequently because of the incomplete resection of the primary tumor, but a small percentage of the cases can be explained by the local spread of the tumor by microvascular embolization or true multifocality [35,36].

A concern could be raised about the recurrence in patients with NSM after PN; several explanations can be considered such as the growth of a new primary tumor, as well as undetected malignancy at the edge of resection of the pathologic specimen (the so-called "false-negative surgical margin"), or the presence of small focal areas of malignancy extending up to 3 mm outside the tumor pseudo capsule, likely within the peritumoral vessels, leading to incomplete resection [35].

7. Treatment of local recurrence after PN

The local tumor recurrence after PN may represent a challenging scenario, since the literature data on the natural history, patient outcome, and prognostic factors are limited, and no standard management strategy has been provided to date [36]. When technically possible, surgery is still the primary curative approach in these patients [37,38]. However, surgical removal may be technically difficult due to several factors, including unfavorable recurrence location, dense fibrosis, stuck renal pedicle, or altered local anatomy resultant from previous PN, as well as patient factors such as advanced age, end-stage renal disease, and multiple comorbidities that may expose to a higher risk of perioperative complications of a second surgery (or salvage surgery) [37,39,40]. In this scenario, an image-guided thermal ablation (TA) may have the potential to circumvent these limitations representing a less invasive alternative to NSS (Table 3).

7.1. TA in patients with local recurrence after PN

In 2018, Zhou et al. [41] reported that TA techniques yielded an overall complete ablation rate of 100%, demonstrating the feasibility of this technique in locally recurrent RCCs despite difficult anatomy or unfavorable tumor location that precluded complete resection. No major (Clavien-Dindo ≥ 3) periprocedural complication was encountered, but a single case of hemorrhage was observed that did not require transfusion or unanticipated escalation of care or other long-term consequence. These data seem to be favorably compared to the about 40% overall complication rate reported for salvage surgery [9,42,43]. One potential explanation for this difference is that TA presents the

Table 3 Studies evaluating the impact of salvage treatment on patients with local recurrence after PN.

Study	Study type	Technique, *n*	Patients/LS, *n*	TS, cm	Success rate[a], %	Complications[b]	Survival outcomes	Treatment of repeat recurrence
Salvage thermal ablation								
Morgan et al. [45], 2013	Case-series	• All P-CA	5/—	2.2	100	• Two self-limiting hematuria	• PFS: 100% at 32 months	• 1 recurrence after 13 months that was treated with repeat ablation
Yang et al. [48], 2013	Retrospective	• P-RFA (14) • P-CA (13) • L-CA (3)	14/33 (all VHL and 12 SK)	2.6	100	• None	• OS: 92% at 37.6 months • CSS: 100% at 37.6 months	• Of 4 recurrences during F/Up, 3 underwent repeat ablation
Hegg et al. [47], 2013	Retrospective	• All P-CA	48/68 (6 VHL and 11 SK)	2.5	100	• Major: 3 (1 pseudoaneurysm underwent embolization, 1 urinary obstruction underwent ureteral stent, and 1 cerebral infarction)	• 3- and 5-year OS: 89% and 81% • 3- and 5-year RFS: 84% and 73%; • 2 patients developed metastases at 19 months	• 5 local recurrences: 2 treated with CA and 3 observed
Monfardini et al. [46], 2015	Retrospective	• P-RFA (6) • LT-RFA (2)	8/16 (3 patients with LS outside the renal fossa, 5 patients with STx before or after RFA)	1.65	100	• None	• Median PFS: 57 months	• 1 local recurrence and 2 lung metastases: All treated with STx
Zhou et al. [41], 2018	Retrospective	• P-RFA (6) • P-CA (4) • P-MWA (1)	8/11	2.8	100	• No major • 1 (9%) asymptomatic hemorrhage (Clavien-Dindo Grade I).	• PFS: 91% at F/Up of 2.5 years • OS: 82% at F/Up of 2.5 years	• 1 case of residual disease at 1-month: Repeat thermal ablation achieving complete response
Salvage nephrectomy								
Liu et al. [43], 2010	Retrospective	• All OPN	25/— (VHL and SK)	—	—	• 5 urine leaks requiring stents in 3 cases • 1 myocardial infarction with death	• 8 (38%) cases of recurrent or *de novo* tumors at 36 months • MFS: 95% at 57 months	—
Watson et al. [50], 2016	Retrospective	• All RAPN	26/26 (19 had hereditary disease)	—	100	• Overall: 57.7% (15/26), • No Grade IV or V	—	—
Autorino [42], 2013	Retrospective	• All RAPN	9/12 (3 SK)	—	100	• Minor: 2 (22%)	• No deaths after 8 months	—
Shah et al. [51], 2018	Retrospective	• All LPN • Cases converted from LPN to OPN: 12 (36%)	33/—	4.5		• Overall: 16 (48%); • Major: 9 (27%)	• No differences in intrarenal RFS ($p=0.5$) between the groups	—
Yoshida et al. [49], 2020	Retrospective and	• s-OPN (11)	11/— (all SK)	—	—	• Minor: 5 (45.5%)	—	—

(*continued on next page*)

Table 3 (*continued*)

Study	Study type	Technique, *n*	Patients/LS, *n*	TS, cm	Success rate[a], %	Complications[b]	Survival outcomes	Treatment of repeat recurrence
	comparative (initial PN *vs.* salvage PN)					• Major: 6 (54.5%) (3 Grade IIIa and 3 Grade IV)		
Martini et al. [9], 2021	Retrospective multicenter	• RAPN (8) • RARN (24)	32/— (12 metachronous)	About 3	—	• s-RAPN: intra-operative: 33%; no postoperative complication • s-RARN: No intra-operative complication; 7% postoperative complication	• Local RFSs were 64% and 82% for s-RAPN and s-RARN, respectively. • 3-year MFR were 80% and 79%, for s-RAPN and s-RARN, respectively.	—

LS, lesions; TS, tumor size; CA, cryoablation; RFA, radiofrequency ablation; MWA, microwave; OPN, open partial nephrectomy; LPN, laparoscopic partial nephrectomy; P-, percutaneous-; L-, laparoscopic; LT-, laparotomic; VHL, von Hippel-Lindau syndrome; SK, solitary kidney; RCC, renal cell carcinoma; CSS, cancer-specific survival; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; STx, systemic therapy; s-, salvage; PN, partial nephrectomy; RAPN, robot-assisted PN; RARN, robot-assisted radical nephrectomy; MFR, metastasis-free rate, F/Up, follow-up; MFS, metastasis-free survival; —, not reported.

[a] Success rate were defined as lacks local recurrence at post-interventional imaging.

[b] Complications were assessed according to Clavien-Dindo classification: minor (<3) vs. major (≥ 3).

technical advantage of image guidance and a low invasive approach with few intracorporeal managements [9,42—44]. Local recurrence can be mapped and targeted using CT guidance, while adjacent non-targeted tissues such as bowel and ureter were protected by utilizing hydro-dissection and retrograde hypoperfusion [41].

Morgan et al. [45] reported a case series of five patients who underwent percutaneous CT-guided cryoablation for locally recurrent RCC after the failure of PN and were followed with serial imaging, laboratory tests, and examination. Regarding the tumor characteristics, four tumors were endophytic, and one was exophytic. The median tumor size was 2.2 cm with nephrometry scores of 8a, 7x, 4p, 6x, 7p, and 6p before cryoablation. Overall, only one patient with a 4 cm endophytic RCC developed a second recurrence measuring 2.9 cm at a median follow-up of 13 months, which was managed successfully with repeat cryoablation without evidence of disease after an additional 19 months. Similarly, Monfardini et al. [46] retrospectively assessed the safety and efficacy of eight patients who were treated with radiofrequency TA for retroperitoneal relapse after open RN or PN for a total of 16 lesions. Disease progression after surgery occurred within a mean time of 57 months with a recurrent tumor size from 5 to 34 mm. Six patients were treated with percutaneous TA, while two with recurrent nodes located on the anterior pancreatic surface underwent laparotomic radiofrequency ablation. All lesions were completely ablated (100% success rate) and disease status was evaluated with CT after 30 days, after 3 months, and every 6 months thereafter. There was no residual enhancement after a mean follow-up of 12 months.

In the largest series to date, Hegg et al. [47] analyzed the outcomes of 48 patients (for 68 ipsilateral tumors) undergoing percutaneous cryoablation of renal tumors after PN between 2003 and 2012. The median maximal diameter of the treated renal recurrence was 2.5 cm. Overall, all the procedures were considered technically successful, but local tumor recurrence occurred in 5 (7.4%) patients during follow-up. It is noteworthy that most recurrences were local and could be treated with re-ablation. Major complications (Grade more than 2) developed in 3 (6.2%) procedures. Interesting to note, the median change in patient estimated glomerular filtration rate after renal cryoablation was 1.5 mL per minute, and no patients required dialysis in the perioperative period, while two with stage 4 chronic kidney disease at the time of ablation became dialysis-dependent at 5 and 23 months after treatment, respectively. This observation validates the role of TA in the setting of recurrent RCC, even when multiple metachronous recurrences occur.

Analyzing a specific cohort of 43 von Hippel-Lindau patients, Yang et al. [48] evaluated the efficacy and safety of probe TA as salvage treatment for renal tumors after previous PN. The authors reported that all procedures were completed without transfusions and intraoperative complications. No early postoperative complications were recorded. With a mean follow-up of 37.6 (range 12—82) months, four patients had a suspicious recurrence on CT or magnetic resonance imaging scan, and in three of them, a re-ablation was performed. Overall survival and CSS were 92% and 100%, respectively.

7.2. PN or RN in patients with local recurrence after PN

Salvage surgery represents a valid option for recurrence after PN, especially when the tumor or patient's characteristics are not ideal for TA [37]. In a previous systematic review, both PN and RN are described as alternative approaches in local relapse after PN [37]. According to our literature research from 2010 to date, only one study assessed the outcomes of RN in this subset of patients using the robotic platform [9]. Overall, six studies analyzed the outcomes of nephrectomy on local recurrence after PN with three of these focused on robotic approach [9,42,43,49–51]. To note, the role of robotic surgery is raising even in challenging scenarios including this setting of patients [52].

In 2013, Autorino et al. [42] demonstrated the feasibility of salvage RAPN in patients with local recurrence who previously underwent ipsilateral NSS. Overall, 12 tumors were removed in nine patients. All surgical margins were negative, and eight of the nine patients with histopathologically proven recurrence were alive and free from the disease within a mean follow-up of 8.3 months. Concerning safety aspects, no intraoperative and two minor complications were reported. Instead, Watson et al. [50] reported an overall complication rate of 57.7% among a cohort of 26 patients who underwent salvage RAPN. Of these, 19.2% presented urine leakage (three patients required urinary stents), and 15.4% needed conversion to open PN. The results of this series suggest a non-negligible rate of complications in the setting of salvage RAPN.

Recently, Martini et al. [9] analyzed the perioperative outcomes of the salvage treatment for local recurrence after prior PN, as well as tumor ablation for RCC with the ambitious aim of standardizing the nomenclature of salvage robot-assisted renal surgery and providing support in clinical decision-making as no guideline or even classification is available to help patients and clinicians in achieving the best-shared decision [9]. Overall, 67 patients underwent salvage robot-assisted renal surgery at nine tertiary referral centers [9]. Of these, 32 (48%) and 35 (52%) patients underwent salvage robotic surgery following PN and TA, respectively. Considering only PN cases, 8 (25%) and 24 (75%) patients underwent salvage RAPN and robot-assisted RN, respectively. The authors reported that salvage RAPN was initially planned and RN was carried out due to surgical complexity in seven cases, and this occurred for a recurrent lesion in the resection bed in six cases [9]. In this subset, no major complications were reported. It is important to note that these results are greatly dependent on the surgeon's experience. Moreover, patient selection may play an important role as salvage surgery is likely to be offered to the fittest patients and in case of high presumed chances of success [9]. Among eight patients undergoing salvage RAPN for a recurrent lesion in the resection bed, excessive bleeding during the resection was observed in two cases, which was eventually controlled using additional sutures and hemostatic material. Among patients undergoing salvage robot-assisted RN, one patient experienced acute kidney injury, which did not require dialysis, accounting for a 7% overall postoperative complication rate. Regarding oncological and functional outcomes at 3-years, local recurrence-free rates were 64% and 82% for salvage RAPN and robot-assisted RN, while metastasis-free rates were 80% and 79%, respectively. The authors concluded that the complication profile is found to be consistent with the complexity of the specific scenario, and the noteworthy intraoperative complication rate is not accompanied by an unsafe postoperative complication profile in the hands of experienced robotic urologists at high-volume institutions. However, further investigations are needed to assess the effectiveness of the salvage techniques in the long-term outcomes and their generalizability and standardization, especially performed with robotic approach [2,53–56].

8. Limitations of the study

Our review is not devoid of limitations, first and foremost due to its non-systematic nature. We did not provide any quantitative synthesis of the collected data. Moreover, the literature study relied only on one dataset, and only English language studies were collected. It might be possible that the current review represents a partial and biased view of currently available evidence on this topic as a consequence of its non-systematic nature. Last, we focused on strategies to diagnose and manage PSM and local recurrence after PN avoiding a deep discussion on oncologic and prognostic factors related to these two aspects and not considering studies without data on management of PSM and local recurrences.

9. Conclusion

Based on data reported in the literature, controversy still exists surrounding the best strategy for management and diagnosis of patients with PSMs as well as local recurrence after PN. The use of intraoperative methods of PSM diagnosis such as FS or US is still debated and many centers did not take them into account with a systematic pathway. However, AS is likely to be the optimal first-line management option for most patients with PSMs as oncological outcomes seem to be comparable to those with negative margins. Immediate or delayed surgical treatment should be proposed as second-line treatment or in selected high-risk patients (high-grade tumors or adverse pathological features). Ablation and salvage surgery both represent valid options in patients with local recurrence after PN. Ablation has a very high primary success rate, but recurrences occur in up to 25% of cases. These can often be managed with repeat ablation. Conversely, salvage PN and RN have fewer recurrences but are associated with a higher complication rate compared to TA. In this scenario, robotic surgery plays an important role in improving salvage PN and RN outcomes. However, the literature addresses these topics through small, retrospective, and highly inhomogeneous studies; in addition, the management of PSM and local recurrence after PN should be more precise than that based on the single surgeons or multidisciplinary-team preference.

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Conflicts of interest

The authors declare no conflict of interest.

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