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Systematic Review

Total adrenalectomy *versus* subtotal adrenalectomy for bilateral pheochromocytoma: meta-analysis

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Abstract

Background: Bilateral pheochromocytomas are rare and often heritable. Total adrenalectomy leads to a definitive oncological cure, with subsequent definitive hypocortisolism. Subtotal adrenalectomy is a possible alternative. The aim of this study was to assess the effects of total adrenalectomy and subtotal adrenalectomy on bilateral pheochromocytoma in terms of post-surgical rate of recurrence, metastatic disease, and steroid dependence.

Methods: Systematic searches in the bibliographic databases PubMed, Embase, and Europe PMC were performed for 1945 to 1 June 2023. PRISMA guidelines were followed and the PICO strategy was applied to English-language studies comparing subtotal adrenalectomy with total adrenalectomy. A random-effects model was used to assess the different outcomes for studies with high heterogeneity. The Newcastle–Ottawa scale and the Risk Of Bias In Non-randomized Studies of Interventions ('ROBINS-I') tool were used to assess quality and risk of bias.

Results: From a total of 12 909 studies, 1202 patients (from 10 retrospective studies) were eligible for the meta-analysis. In six studies, including 1176 patients, the recurrence rate after subtotal adrenalectomy and total adrenalectomy was 14.1 *versus* 2.6 per cent respectively (OR 4.91, 95 per cent c.i. 1.30 to 18.54; $P = 0.020$; I^2 72 per cent). In nine studies, including 1124 patients, the rate of post-surgical steroid dependence was 93.3 *versus* 11.6 per cent after total adrenalectomy and subtotal adrenalectomy respectively (OR 0.003, 95 per cent c.i. 0.0003 to 0.03; $P < 0.00001$; I^2 66 per cent). Based on two studies, including 719 patients, no differences were evident regarding the occurrence of post-surgery metastatic disease.

Conclusion: Subtotal adrenalectomy leads to less post-surgical primary adrenal insufficiency, but leads to a higher postoperative recurrence rate. Future prospective randomized studies, with clear eligibility criteria, are needed to confirm these results.

Introduction

The WHO classification defines pheochromocytoma as adrenal tumours that store and release catecholamines in excess[1]. Bilateral pheochromocytomas may present either synchronously or metachronously and occur predominantly as heritable diseases, such as multiple endocrine neoplasia type 2 (MEN 2) caused by germ-line mutations of the *RET* proto-oncogene, von Hippel-Lindau (VHL) disease, and the pheochromocytoma-paraganglioma syndromes caused by mutations in the succinate dehydrogenase genes[2]. In recent years, increasing numbers of putative genes (including *TMEM127*, *FH*, and *MAX*)[3,4] have been identified and the rate of pheochromocytomas arising within a genetic background is considered higher than 30 per cent[5].

The standard definitive treatment for pheochromocytoma is complete resection, even bilateral total adrenalectomy (TA) in bilateral variants. However, this strategy results in permanent primary adrenal insufficiency, with the need for long-term corticosteroid replacement therapy and a lifelong risk of Addisonian crises[6]. Subtotal adrenalectomy (SA) entails the partial removal of the adrenal gland (including the tumour) instead of the entire organ and potentially preserves adrenal cortical tissue and function, thus avoiding lifelong steroid replacement[1,7]. This surgical procedure, however, exposes patients to the risk of recurrent pheochromocytoma arising from the remnant medullar adrenal tissue[8,9].

The choice between TA and SA for bilateral pheochromocytomas remains debatable, as the quality of evidence supporting the choice of either surgical management is low[6].

Although some series have demonstrated favourable short-term outcomes for SA, uncertainty remains, because the risk of metastatic pheochromocytomas can be greater than 10 per cent, especially in genetic variants, such as succinate dehydrogenase complex iron sulphur subunit B (*SDHB*)-related tumours, and the potential for developing ipsilateral recurrent

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pheochromocytomas in the remnant may occur even in the absence of metastatic disease[9,10].

The choice of the right surgical approach should be carefully balanced between the potential prevention of Addisonian crises and the risk of metastatic pheochromocytomas and development of a new or recurrent ipsilateral or contralateral pheochromocytoma. Therefore, the aim of this systematic literature review and meta-analysis was to compare the oncological and functional post-surgical outcomes between SA and TA.

Methods

The study was registered in PROSPERO, the international prospective register of systematic reviews (registration number CRD42021250004). A literature search was performed based on the PRISMA[11] and Meta-analysis Of Observational Studies in Epidemiology ('MOOSE')[12] guidelines. The PRISMA checklist is listed in *Table S1*.

To identify all relevant publications regarding the comparison between SA and TA for patients with bilateral pheochromocytoma, systematic searches in the bibliographic databases PubMed, Embase, and Europe PMC were performed for 1945 to 1 June 2023. Search terms included controlled terms (Medical Subject Headings (MeSH) in PubMed and Emtree in Embase) combined using Boolean operators.

Any English-language original reports describing direct comparison of SA *versus* TA were included.

Studies that reported either only SA or TA were excluded.

No restrictions on length of follow-up after surgery were applied. The additional exclusion criteria were as follows: studies without sufficient data for comparison (reviews, guidelines, conference proceedings, abstracts, letters, and comments); and studies that included only patients with metastatic tumours. Case series were considered only if they contained relevant results.

Adrenalectomy was considered as subtotal, both when the first surgical approach was performed as SA bilaterally, as well as when unilateral TA was done for one side plus contralateral SA, synchronously or metachronously. Cases reporting a comparison between SA and TA + autotransplantation of cortical tissue were excluded. Moreover, only studies reporting cases of bilateral pheochromocytoma were considered; cases of isolated paragangliomas were excluded.

The aim of this review was to elucidate whether the risk of recurrence and functional post-surgical outcomes were different between SA and TA for patients affected by bilateral pheochromocytomas.

The PICO terms were defined as follows: (P)atients, people with bilateral pheochromocytoma who were candidates for adrenalectomy; (I)ntervention, adrenal surgery, either SA or TA; (C)omparison, SA *versus* TA (by any method of surgery (laparotomy, laparoscopy, or robotic); and (O)utcomes, functional outcomes (metabolic evaluations of steroid dependence), recurrence rate (local or contralateral), and risk of metastasis.

The following keywords were used for the search: subtotal adrenalectomy OR total adrenalectomy AND pheochromocytoma; partial adrenalectomy OR total adrenalectomy AND pheochromocytoma; and cortical sparing adrenalectomy OR total adrenalectomy AND pheochromocytoma. The complete search strategy is available in *Table S2*.

Initially, the titles of retrieved studies were screened independently by two authors (M.B. and M.F.) and irrelevant studies were excluded. Then, the same authors (M.B. and M.F.) and a third author (D.S.) screened the abstracts. Finally, the full texts of selected studies were retrieved and the compliance with the inclusion criteria was confirmed by the same authors (M.B., M.F., and D.S.). Eligible studies were then integrated into a database for meta-analysis. Data from the selected studies were extracted by the three authors (M.B., M.F., and D.S.). Any disagreement between the authors was resolved by the senior author (M.I.).

Data extracted from incorporated studies included study sample size and demographic data of patients, including age and gender, tumour size, follow-up surgery, and outcomes, including functional and oncological outcomes. Genetic characterization was also collected when available.

The outcomes of interests were: primary adrenal insufficiency and functional outcomes (either based on serial hormonal evaluation (adequate adrenocortical function based on postoperative adrenocorticotropic hormone ('ACTH') stimulation testing and morning cortisol) or on steroid dependence (considered as chronic steroid therapy after the first surgical treatment); recurrence rate (with recurrence of pheochromocytoma defined as the new development of elevated urinary catecholamine levels and the presence of a radiologically documented new intra-abdominal mass in the adrenal gland, ipsilateral, or contralateral, after the first surgical treatment); and risk of metastases (report of metastatic disease after the first surgical treatment).

Statistical analysis

Outcome data for steroid dependence, recurrence rate, and risk of metastases after the first surgical treatment were pooled using Review Manager version 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and presented as forest plots. Heterogeneity was assessed by calculating the I^2 index. For low heterogeneity (I^2 below 50 per cent), a fixed-effect model was used for meta-analysis. For high heterogeneity (I^2 over 50 per cent), a random-effects model was used for meta-analysis. I^2 above 75 per cent was considered substantial and no meta-analysis was performed. In this review all outcomes of interest were dichotomous.

A statistically significant difference was observed at a two-tailed 0.05 level for the hypothesis and at 0.10 for heterogeneity testing.

Quality assessment and risk of bias

Quality was assessed using the Newcastle–Ottawa scale[13], in separate domains of sampling, measurement, and analysis. The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool[14] was used to score the overall final risk of bias.

This was done by two authors (M.B. and M.F.). Any disagreements were resolved by discussion or by involving two other authors (D.S. and M.I. (the senior author)). The ROBINS-I tool consists of seven domains (bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, bias in selection of the reported result, and overall bias).

Results

The initial search resulted in a total of 12 909 records. After removal of 3895 duplicates and screening all titles and abstracts, a total of 30 papers were assessed in full for

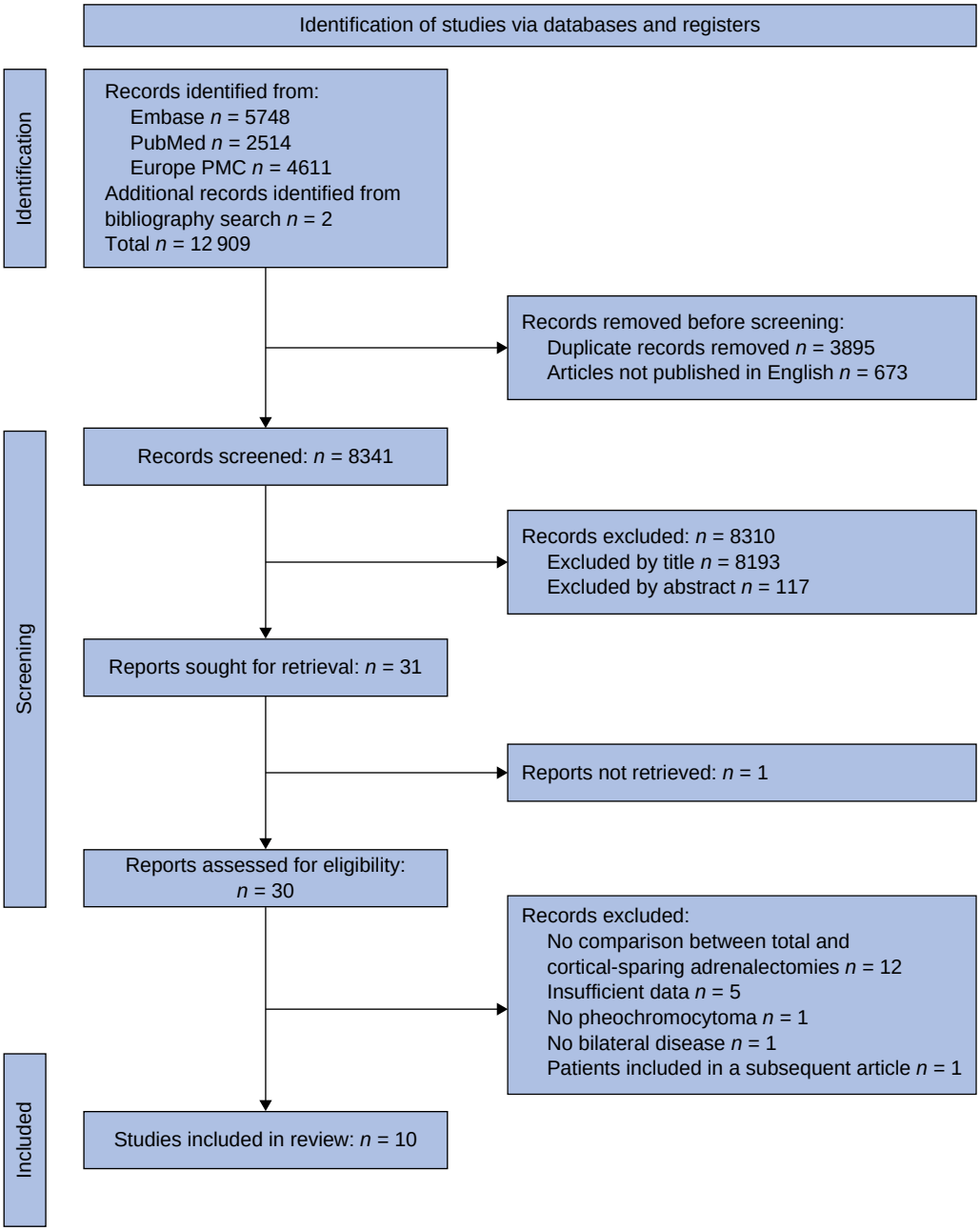

Fig. 1 PRISMA[11] flow chart

inclusion; 20 were excluded, resulting in a total of 10 studies for analysis[2,7,15–22] (*Fig. 1* and *Table S1*). All 10 articles were observational cohorts, representing a total of 1279 patients. A total of 1202 patients affected by bilateral pheochromocytoma were eligible for the meta-analysis. No prospective randomized studies were available. Two studies were multicentre studies[2,21] and eight studies were monocentre studies[7,15–20,22].

Patient and study characteristics are summarized in *Table 1*. The estimated mean duration of follow-up ranged from 12.7 to 160.8 months. Mean age ranged from 31 to 51 years. Tumour size ranged from 1.5 to 12 cm, with no differences between SA and TA reported (mean(s.d.) size of 3.19(1.3) cm (range 0.7–5.8 cm) and 3.9(2.7) cm (range 1.1–12 cm) respectively; $P > 0.05$). Bilateral pheochromocytomas presented synchronously in most of the cases.

SA was the treatment of choice in 10–67 per cent of the study population. The genetic mutational background of enrolled patients is listed in *Table S3*.

Main outcomes

Steroid dependence

Nine of the included studies[2,15–22] reported data about steroid therapy dependence, for a cohort of 1124 patients. The pooled effect of post-surgical steroid dependence highlighted a higher risk for TA compared with SA (93.3 *versus* 11.6 per cent respectively; OR 0.003, 95 per cent c.i. 0.0003 to 0.03; $P < 0.00001$; I^2 66 per cent) (*Fig. 2*). For a cohort of 145 patients, no adrenal crises were reported in the SA pooled population *versus* a rate of 6.1 per cent in the TA pooled population

Table 1 Study characteristics and demographic information

Reference, country, year, design	Sex (M : F), % M	Age (years)	Tumour size (cm)	Pheochromocytoma (number of patients)	Synchronous *versus* metachronous, % synchronous	Subtotal adrenalectomy	Total adrenalectomy	Follow-up (months)	Overall risk of bias (ROBINS-I)[14]
Asari *et al.*[15], Austria, 2006, retrospective	8 : 17, 47	47.7(17.8)*	NR	10	5 *versus* 5, 50	1 (10)	9 (90)	137.3(119.5)*	Serious risk
Simforoosh *et al.*[19], Iran, 2020, retrospective-prospective	NR	NR	NR	6	6 *versus* 0, 100	2 (33)	4 (67)	78	Serious risk
Goretzki *et al.*[16], Austria, 1996, retrospective	4 : 14, 29	42 (25–54)†	range (1–4.5)	10	7 *versus* 3, 70	3 (33)	7 (67)	59 (5–182)†	Serious risk
Nockel *et al.*[18], USA, 2018, retrospective	60 : 48, 56	42 (5–76)†	NR	68	12 *versus* 56, 18	14 (21)	54 (79)	NR	Critical risk
Castinetti *et al.*[21], multicentre study, 2014, retrospective	252 : 311, 45	37(12.8)* range (12–89)	NR	345	244 *versus* 95, 71	82 (24)	257 (76)	156(11.6)*	Serious risk
Neumann *et al.*[2], multicentre study, 2019, retrospective	325 : 300, 52	30 (22–40)†	NR	625	401 *versus* 224, 64	324 (52)	301 (48)	96 (36–300)†	Serious risk
Kittah *et al.*[17], USA, 2020, retrospective	46 : 48, 49	31 (4–70)†	3.0 (0.6–12.0)†	94	75 *versus* 19, 80	18 (19)	76 (81)	102 (0–624)†	Serious risk
Scholten *et al.*[20], The Netherlands, 2011, retrospective	37 : 24, 61	33.0(12.7)*	NR	31	NA	9 (29)	22 (71)	160.8(129.6)*	Serious risk
Jansson *et al.*[22], The Netherlands, 2006, retrospective series	5 : 7, 45	51	NR	12	10 *versus* 2, 80	8 (67)	1 (33)	12.7 (1.5–26)†	Serious risk
Shirali *et al.*[7], USA, 2023, retrospective	31 : 47, 53	32.5 (26.2–40.6)†	2.5 (1.5–3.9)†	78	NR	62	52	81	Serious risk

Values are *n* (%) unless otherwise indicated. *Values are mean(s.d.). †Values are median (range). ROBINS-I, Risk Of Bias In Non-randomized Studies of Interventions; NR, not reported.

(OR 0.62, 95 per cent c.i. 0.12 to 3.14; $P = 0.570$; I^2 0 per cent)[15–17,20] (*Fig. 3*).

Rate of recurrence

Six studies[2,7,17,20–22] reported data about the recurrence rate, for a cohort of 1176 patients. The pooled results showed a higher risk of recurrence in SA *versus* TA (14.1 *versus* 2.6 per cent respectively; OR 4.91, 95 per cent c.i. 1.30 to 18.54; $P = 0.020$; I^2 72 per cent) (*Fig. 4*). Only one study[2] provided data on time to recurrence in both SA and TA groups and there was no difference between the treatment groups (OR 7.22, 95 per cent c.i. 4.39 to 18.83; $P = 0.220$).

Risk of metastases

Only two articles[2,17] reported data about metastatic disease after the first surgical treatment, for 719 patients with bilateral pheochromocytoma. There were no differences for this outcome between SA and TA (the pooled results were 2.6 *versus* 2.0 per cent respectively; OR 2.05, 95 per cent c.i. 0.70 to 6.00; $P = 0.190$; I^2 0 per cent) (*Fig. 5*).

Quality assessment and risk of bias

Quality assessment of included studies according to the Newcastle–Ottawa scale[13] is presented in *Table S4* and *Table S5*. The overall final risk of bias of the included studies was also tested through the ROBINS-I tool risk of bias[14] (*Table 1* and *Table S6*) and considered moderate to critical, based only on observational studies.

Furthermore, most of the studies included in the meta-analysis had a significant risk of bias as an appropriate analysis method that controlled for confounding was not used. Some of the studies described the outcomes selected without the purpose of comparing SA or TA[15–18]. Thus, results were not always clear and had sometimes been extrapolated from other characteristics of the population analysed. All studies included in the meta-analysis were non-randomized and retrospectively designed. Therefore, the allocation of patients to SA or TA surgical treatment was made by different surgeons, whose clinical experience in adrenal cortex-sparing surgery could differ, leading to an important bias of patient selection and allocation.

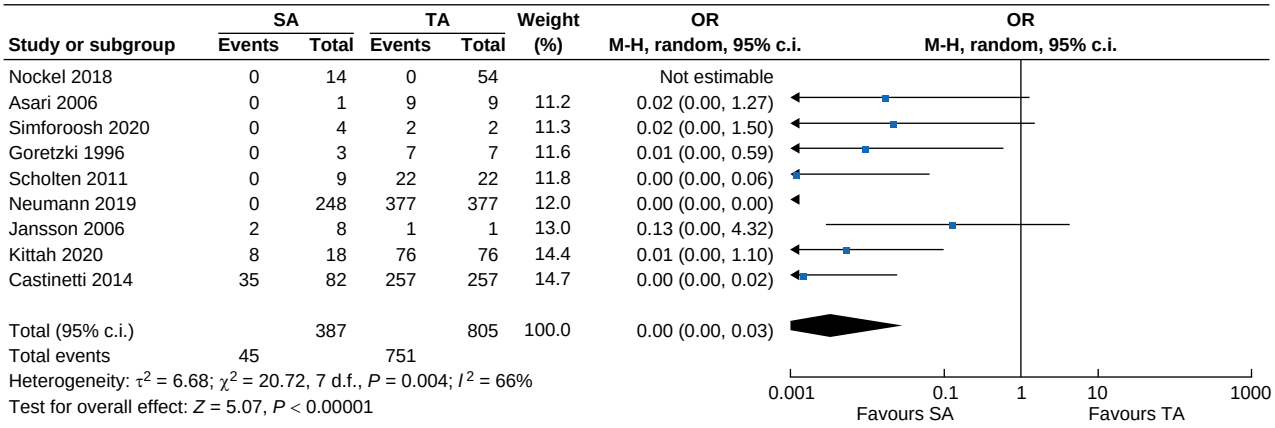

Fig. 2 Forest plot comparing steroid dependence between subtotal and total adrenalectomy

A Mantel–Haenszel fixed-effects model was used for meta-analysis. ORs are shown with 95% c.i. SA, subtotal adrenalectomy; TA, total adrenalectomy; M-H, Mantel–Haenszel.

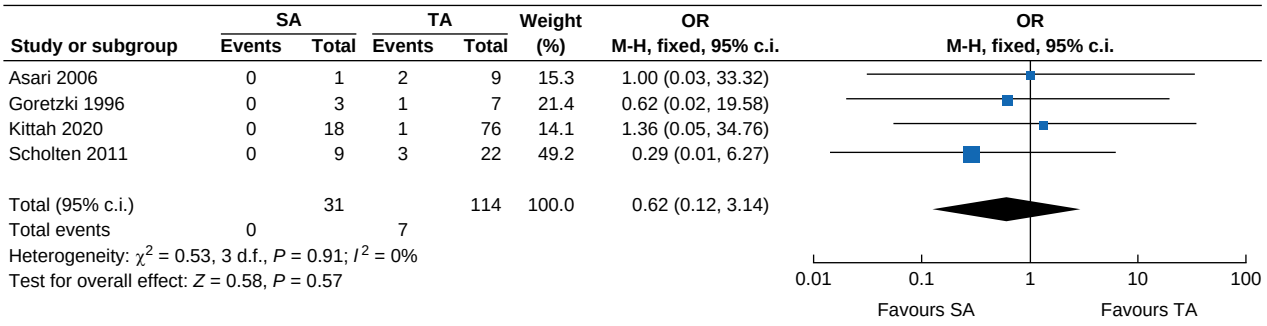

Fig. 3 Forest plot comparing adrenal crises between subtotal and total adrenalectomy

A Mantel–Haenszel fixed-effects model was used for meta-analysis. ORs are shown with 95% c.i. SA, subtotal adrenalectomy; TA, total adrenalectomy; M-H, Mantel–Haenszel.

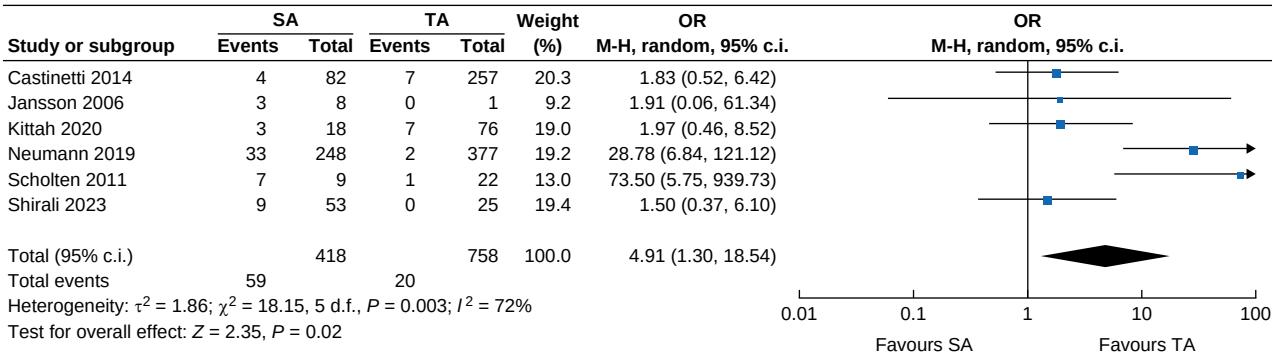

Fig. 4 Forest plot comparing rate of recurrence between subtotal and total adrenalectomy

A Mantel–Haenszel random-effects model was used for meta-analysis. ORs are shown with 95% c.i. SA, subtotal adrenalectomy; TA, total adrenalectomy; M-H, Mantel–Haenszel.

Discussion

Patients with bilateral pheochromocytomas have been frequently treated with TA. SA was introduced into clinical practice more than 20 years ago and has been a relatively underused procedure[2,15,23]. This analysis reveals that SA might be preferable in patients undergoing surgery for bilateral pheochromocytomas, because of its advantages in reducing and avoiding chronic steroid dependence and associated side effects. These benefits should be carefully weighed against an increased recurrence rate, on an individual basis, taking into consideration the genetic background and a patient's preferences. SA offers a chance to avoid complete dependence on steroids, which is the inevitable consequence of bilateral adrenal removal[20]. Several adverse side effects are encountered with chronic steroid therapy, such as premature osteoporosis, complications of hypertension, and diabetes. Other common side effects are mood changes, diarrhoea, abdominal distension, dyspepsia, increased appetite, peptic ulcers, hirsutism, immunosuppression, hypertension, oedema, and hypokalaemia, with a major impact on quality of life[2,24].

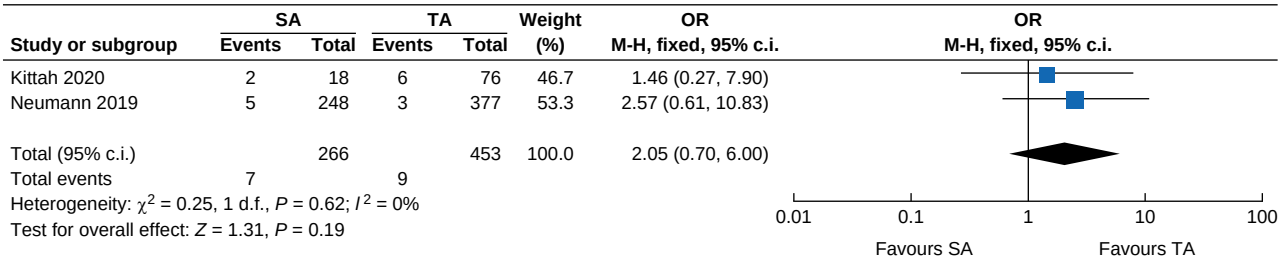

Fig. 5 Forest plot comparing risk of metastases between subtotal and total adrenalectomy

A Mantel–Haenszel fixed-effects model was used for meta-analysis. ORs are shown with 95% c.i. SA, subtotal adrenalectomy; TA, total adrenalectomy; M-H, Mantel–Haenszel.

Moreover, even in patients with good therapeutic compliance, an insufficient steroid dose in addition to a stressful event can have irremediable negative effects. Addisonian crises are associated with an approximately 6 per cent risk of death[7,23]. In this context, the present meta-analysis confirms that SA offers a clear advantage compared with TA in terms of steroid dependence, as all patients undergoing bilateral TA became entirely steroid dependent, as expected. No differences were registered in terms of Addisonian crises, probably due to the small number of patients in the sample.

Similarly, a recent study reported that SA can reduce the need for steroid replacement therapy and carries a low risk for recurrence, but it was mainly based again on analysis of retrospective studies with small sample sizes[9].

Neumann *et al.*[2] presented the largest comparative retrospective study on outcomes of treatment in patients with bilateral pheochromocytomas based on a multicentre prospectively enrolled series of 625 patients (most of them harbouring MEN 2 and VHL familial disease). After SA, recurrent pheochromocytoma occurred in 13 per cent of patients in the spared ipsilateral adrenal gland. However, it should be underlined that these results were recorded in a population with a median age of 30 years, at a median follow-up limited to 8 years, with unknown postoperative outcomes at a prolonged follow-up in young patients; thus, the cohort that has more weight in this meta-analysis in terms of number of patients seems to be affected by an important population selection bias.

Moreover, there are still uncertainties about adequate adrenal-sparing techniques. It is mostly suggested that free margins of at least 3–5 mm are necessary to attain adequate radicality in the case of SA[9,24–27]. Extracapsular dissection and mobilization of the pheochromocytoma should be performed, avoiding any pheochromocytoma capsular rupture, which can lead to tumoral spread and recurrence. However, it should be considered that a recurrence may occur even in the case of complete resection of the tumour, as it may arise from the adrenal medulla in the remnant after SA. Furthermore, the amount of residual adrenal cortical tissue that needs to be left *in situ* to maintain acceptable cortical function, while ensuring adequate tumour clearance, is still widely debated[9]. It is argued by some that acceptable function and drainage of the residual gland can be achieved thanks to the preservation of the main adrenal vein or through careful preservation of the minor venous plexuses within the retroperitoneal space[9,26–29].

This suggests that there may be significant variability in the effectiveness of adrenal-sparing surgical techniques among different centres, with subsequent strong limitations regarding any conclusions made when comparing results from different series. Unfortunately, not all of the included studies described how the subtotal dissection was technically achieved and the completeness of pheochromocytoma excision was not defined.

Intraoperative ultrasonography might be an important adjunct tool to recognize adrenal nodules and to allow safe SA and a complete tumour resection. Recently, the use of indocyanine green fluorescence opened up new frontiers in parenchymal-sparing surgery, as it might clearly distinguish the adrenal medulla (that appears hypofluorescent) from adrenocortical tissue (that appears spontaneously hyperfluorescent) and may show the vascularization and vitality of the remnant[30,31].

An oncological complete resection is indeed only achieved if no chromaffin tissue is left *in situ* and, even in expert hands, this objective may not be easy to achieve. However, it should also be considered that a recurrence may occur in extra-adrenal tissue such as paragangliomas in the case of genetic disease and that risk is not lowered by performing TA; for these reasons, in the present study, all papers including paragangliomas alone were excluded from the analysis.

Next-generation sequencing has allowed rapid, accurate testing of tumour related-genes, including those for bilateral pheochromocytoma-related syndromes[18,32]. Castinetti *et al.*[21] showed in a multicentre study, which was included in the present meta-analysis, that almost half the cohort of patients with *RET* germ-line mutations presented with bilateral pheochromocytoma since the initial diagnosis, with an extremely low malignancy rate. Thus, these data suggest that, in patients with *RET* germ-line mutations without evident signs of malignancy, SA might be the preferred option. Similarly, in VHL-related pheochromocytomas, bilateral involvement occurs very often, either synchronously or metachronously, with a very low risk of malignancy[2,18,33], suggesting that minimally invasive SA is indicated to preserve cortical function and avoid lifelong steroid replacement[18,21,33,34]. In contrast, *SDHB*, *MAX*, *TMEM127*, and *FH* germline mutations confer a higher risk of recurrence, extra-adrenal disease, and/or metastatic disease. Therefore, more extended approaches (including even laparotomic adrenalectomy and regional lymphadenectomy in the case of suspected malignancy) might be preferred in patients with these syndromes[18,32]. Unfortunately, the studies included in the present meta-analysis did not report sufficient data to run, as was the intention at the beginning, a subgroup analysis based on genetic characteristics and/or type of surgery (laparotomic, laparoscopic/robotic, and retroperitoneoscopic). In summary, the present study demonstrates that SA reduces the need for steroid replacement, but leads to a higher rate of recurrence, with an eight-fold higher OR. However, there are not sufficient comparative data regarding long-term follow-up

and overall survival. Interestingly, from the present study, SA does not cause a higher risk of metastatic disease in comparison with TA; however, this outcome has been calculated only on data from two studies with a relatively small population.

Moreover, according to the WHO in 2022[1], metastatic pheochromocytoma is defined as an extra-adrenal tumour located in an area where paraganglia do not normally occur (that is lymph nodes or bone). So, it could be difficult to distinguish a paraganglioma from a real metastasis; thus, the risk of metastasis occurrence could have been overestimated for both SA and TA pooled populations.

The present meta-analysis has some limitations. The review is based on an analysis of retrospective studies; thus, patient allocation bias is the first big issue to consider and may explain a certain heterogeneity in result distribution and adds a level of difficulty in the correct interpretation of target data. Furthermore, there is a high level of heterogeneity among the studies included in the meta-analysis in terms of population numbers and outcome definitions. Moreover, not all of the included studies reported data regarding the selected outcomes and, in some cases, it was not possible to clearly allocate events to a specific category. An important aspect is that the selected studies reported different follow-up durations, a wide range of surgical techniques for SA, and various genetic backgrounds, factors that significantly influence the analysed outcomes. In fact, the risk of recurrence potentially increases according to the duration of the follow-up; moreover, the risk of recurrence and metastatic behaviour are significantly increased depending on the implicated genes (as may occur in *SDHB*-related disease)[35]; however, information regarding the genetic background is missing in most published series.

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Author contributions

Donatella Schiavone (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing—original draft, Writing—review & editing), Mattia Ballo (Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing—review & editing), Marco Filardo (Data curation, Investigation, Methodology, Software, Validation, Visualization, Writing—review & editing), Silvia Dughiero (Investigation, Resources, Validation, Visualization, Writing—review & editing), Francesca Torresan (Investigation, Validation, Visualization, Writing—review & editing), Gian Paolo Rossi (Supervision, Validation, Visualization, Writing—review & editing), and Maurizio Iacobone (Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing)

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

All data are included in the article/Supplementary material. Further enquiries can be directed to the corresponding author.

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