Original Article

Effects of somatostatin analogs on uptake of radiolabeled somatostatin analogs on imaging: a systematic review and meta-analysis

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Background: The imaging of somatostatin receptors (SSTRs) plays a significant role in imaging neuroendocrine tumors (NETs). However, there has been no clear definition on whether it is necessary to withdraw somatostatin analogs (SSAs) before SSTRs imaging. We aimed to assess whether nonradioactive SSAs affect the uptake of radiolabeled SSAs on imaging for NETs patients.

Methods: The databases of PubMed, Embase, and Web of Science (WoS) were searched until March 12, 2022 to identify eligible studies. Maximum standardized uptake values (SUVmax) in tumor and normal tissues were extracted, pooled, and compared before and after SSAs treatment. The change of tumor-to-background/liver ratio was also described. The quality of each study was assessed using the revised Quality Assessment of Diagnostic Accuracy Studies-2 tool.

Results: A total of 9 articles involving 285 patients were included and 5 studies using Gallium-68-labeled [1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid]-D-Phe^{1}-Tyr^{3}-Thr^{8}-octreotide (^{68}Ga-DOTATATE) were used for pooled evaluation. We found a significantly decreased SUVmax in the liver (9.56±2.47 *vs.* 7.62±2.12, P=0.001) and spleen (25.74±7.14 *vs.* 20.39±6.07, P=0.006) after SSAs treatment whereas no significant differences were observed in the uptake of thyroid, adrenal, and pituitary gland. For either primary tumor sites or metastases, the SUVmax did not change significantly before and after SSAs treatment. The tumor-to-liver/background ratio increased following SSAs therapy. High heterogeneity was observed across the studies, mainly due to inherent diversity of study design, sample size, and scanning technique.

Conclusions: Based on current evidence, long-acting SSAs therapy before imaging has no effect on the uptake of radiolabeled SSAs at tumor primary sites and metastatic lesions, but results in a significant reduction of uptake in the liver and spleen. These findings may implicate the unnecessary discontinuation of SSAs before radiolabeled SSAs imaging.

Keywords: Neuroendocrine tumor (NET); somatostatin analogs (SSAs); somatostatin receptor imaging; uptake; meta-analysis

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Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors that occur rarely in comparison with other malignant tumors (1). The incidence of NETs only contributes 0.5% of all malignancies (2). NETs originating from neuroendocrine cells disseminate throughout the body, and the most common site is the gastrointestinal tract, followed by the lung and pancreas (3). Somatostatin receptors (SSTRs), as members of the 7 transmembrane segment receptor superfamily, are overexpressed on most NETs and can bind somatostatin with high selectivity and affinity (4,5). Thus, SSTRs have become the therapeutic and diagnostic target in clinical conditions. Due to the low metabolic stability of natural somatostatin, many synthetic analogs such as octreotide, pasireotide, and lanreotide have been developed to improve the stability (6,7).

Iodine-123, Indium-111 (^{111}In), and Technetinum-99m (^{99m}Tc)-labeled somatostatin analogs (SSAs) scintigraphy were the initial methods to visualize SSTRs-positive NETs with a detection rate ranging from 50% to 100% (8-11). However, these SSTRs imaging methods present some limitations in detecting liver lesions or small lesions because of the liver physiological uptake and the low resolution of gamma camera (12,13). Gallium-68 (^{68}Ga)-labeled [1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid]-conjugated SSAs (^{68}Ga-DOTA-conjugated SSAs) such as ^{68}Ga-[DOTA-D-Phe^{1}-Tyr^{3}-Thr^{8}]-octreotide (^{68}Ga-DOTATATE), ^{68}Ga-[DOTA-D-Phe^{1}-Tyr^{3}]-octreotide (^{68}Ga-DOTATOC), and ^{68}Ga-[DOTA-D-Phe^{1}-1-Nal^{3}]-octreotide) (^{68}Ga-DOTANOC) were subsequently developed and opened a new horizon in imaging NETs. Positron emission tomography/computed tomography (PET/CT) with ^{68}Ga-DOTA-conjugated SSAs provides higher spatial resolution and more functional and anatomic data compared to single photon emission computed tomography (SPECT) and conventional imaging. Meanwhile, it also has better diagnostic sensitivity and specificity than fluorine-18 [^{18}F]-fluorodeoxyglucose (^{18}F-FDG) PET/CT for detecting NETs, resulting in significant management change (14-16). Up to now, ^{68}Ga-DOTA-conjugated SSAs PET/CT has been widely used in primary tumor localization, metastatic disease detection, and response monitoring, as well as predicting the treatment response for NET patients (17,18).

As the first-line therapy for functionally active NETs, SSAs play a prominent role in controlling hormonal symptoms and reducing tumor growth (5,19). Since nonradioactive SSAs treatment and SSTRs imaging involve the same receptors, high-dose SSA treatment prior to imaging could theoretically interfere with the uptake of radiolabeled SSAs by receptor internalization and saturation (20). Both the European Association of Nuclear Medicine (EANM) procedure guideline for ^{68}Ga-DOTA-conjugated peptides PET/CT and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) concept in ^{68}Ga-DOTATATE PET/CT recommend the time interval of 3–4 or 4–6 weeks between long-acting SSAs treatment and ^{68}Ga-DOTA-conjugated peptides PET/CT to avoid possible SSTR blockade (15,21). However, no clear or strong evidence has been provided to confirm the necessity of SSAs withdrawal before PET imaging. In contrast, recent studies investigating the effect of nonradioactive SSAs on uptake of ^{68}Ga-DOTA-conjugate peptides found reduced uptake in normal tissues, stable uptake in tumor sites, and improved tumor-to-background ratio (22-24). Therefore, in this systematic review and meta-analysis, we aimed to assess whether prior SSAs treatment affects the uptake of radiolabeled SSAs in normal organs and tumor lesions for patients with NETs. We present this article in accordance with the PRISMA-DTA reporting checklist (25) (available at https://qims.amegroups.com/article/view/10.21037/qims-23-477/rc).

Methods

Our study was registered on the international prospective register of systematic reviews (PROSPERO) (CRD42022321650).

Search strategy

A literature search of the databases of PubMed, Embase, and Web of Science (WoS) was performed until March 12, 2022. Keywords were based on the following: ("neuroendocrine tumor" OR "NETs") AND ("somatostatin receptor imaging" OR "somatostatin receptor Scintigraphy" OR "PET" OR "photon emission tomography" OR "SPECT" OR "single photon emission computed tomography") AND ("somatostatin analogs" OR "SSA" OR "Lanreotide" OR "octreotide" OR "Pasireotide" OR "DOTATATE" OR "DOTATOC" OR "DOTANOC").

Study selection

Studies investigating SSTR imaging before and after

the commencement of SSA therapy were evaluated. The inclusion criteria were as follows: (I) clinical original studies regarding the alteration of uptake in normal organs and tumors between two SSTR images, which were performed prior to and after SSA treatment. (II) Patients had been confirmed with histologically well-differentiated NETs. Studies irrelevant to the topic were excluded, and case reports, conference abstracts, letters, editorial materials, and reviews were also excluded. When data overlapped among studies, the study with the most details was chosen. The included studies were written in English and performed on humans.

Data extraction

Two reviewers independently extracted data from the eligible studies about study characteristics (i.e., first author, publication year, country, study design) and patient characteristics (i.e., patient population, age, clinical setting, SSAs treatment, uptake characteristics, time intervals). Technical details (i.e., imaging modality, ligand, and injection dose) and any data regarding the tracer uptake in normal tissues and tumor lesions before and after SSAs treatment were also collected.

Quality assessment

The quality of the included studies was independently assessed by two reviewers according to the revised Quality Assessment of Diagnostic Accuracy Studies-2 tool (QUADAS-2 revision) (26). The QUADAS-2 revision was used to evaluate the risk of bias for the following criteria: patient selection, first scan, second scan, and flow/timing, whereas applicability concerns were assessed for patient selection, first scan, and second scan (Table S1). Any discrepancies were resolved by discussion with a third reviewer.

Statistical analysis

The maximum standardized uptake value (SUVmax) of normal tissues including liver, spleen, adrenal glands, thyroid, and pituitary gland was extracted and individually pooled using a random effects model. Similarly, the uptake of tumor lesions categorized according to anatomical site (primary sites, liver, lymph nodes, and bone metastases) was also individually analyzed. Further, the measurements were compared between pretreatment and posttreatment scan. Stata version 15.0 (StataCorp., College Station, TX, USA) was used to conduct meta-regression analyses based on a linear mixed model for summarized mean SUVmax with 95% confidence intervals (CIs). The RevMan 5.3 software (Cochrane Collaboration, Copenhagen, Denmark) was used to evaluate the risk of bias. Heterogeneity between the studies was evaluated using the I^2 statistic, and the I^2 value greater than 50% was indicative of substantial heterogeneity (27).

Results

Literature search

The flow chart showed an overview of the search and selection process (*Figure 1*). A total of 6,928 records were identified, and 2,701 records were removed as duplication. After reviewing the title and abstract, 4,210 articles were excluded because they were cases, reviews, letters, conference abstracts, basic studies, or studies relevant to disease diagnosis or treatment. A total of 8 articles were excluded after full-text evaluation. Finally, 9 articles were eligible for this systematic review and meta-analysis (22-24,28-33).

Study description

Table 1 summarizes the main characteristics of the included 9 studies. Among them, 6 studies were performed in Europe, 2 studies in Australia, and 1 in China; 3 studies were performed prospectively, whereas 6 studies had a retrospective study design; 7 studies involved intraindividual research, 1 interindividual research, and 1 combined inter- and intra-individual study design. *Table 2* shows the imaging modalities of SSTRs among the 9 studies. The uptake of ^{68}Ga-DOTA-SSAs was assessed in 6 studies, especially ^{68}Ga-DOTATATE in 5 studies, whereas the other 3 studies investigated the uptake of ^{111}In or ^{99m}Tc labeled SSAs. The injection activity of radiolabeled SSAs was heterogeneous and contained both weighted-based and fixed activities.

Quality assessment

Following the revised QUADAS-2 tool, we assessed the quality of included studies (*Figure 2*). For interindividual design studies, SSTRs imaging of the SSAs untreated group was regarded as the first scan while that of the SSAs treated group as the second scan. For intraindividual studies, pretreatment and posttreatment SSTRs imaging

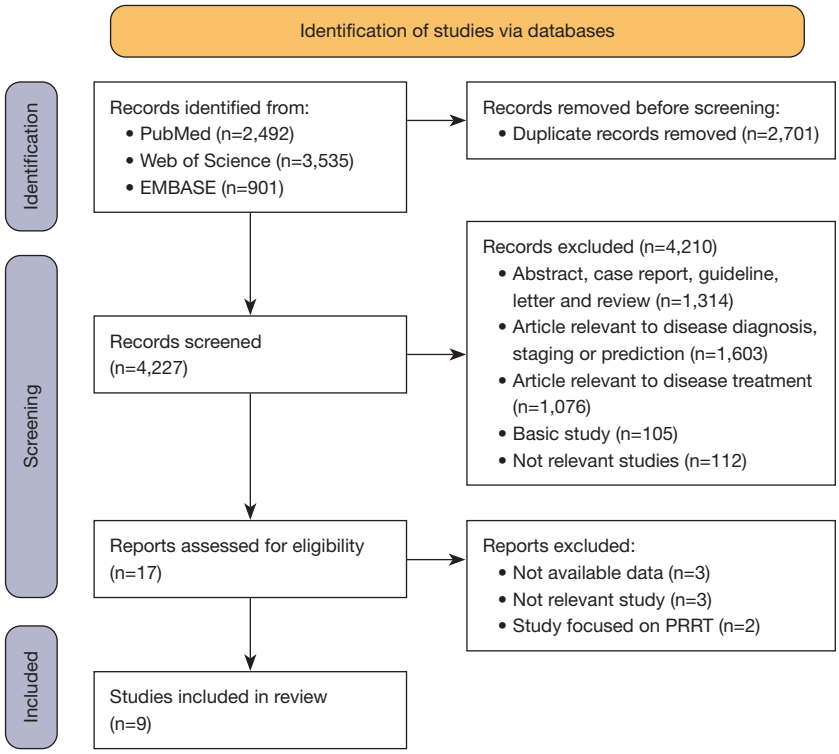

Figure 1 Flow chart of study selection. PRRT, peptide receptor radionuclide treatment.

were defined as first and second scan, respectively. Almost all studies had a low risk of bias in patient selection. Only 1 study had an unclear risk of bias in patient selection and applicability concerns because 3 patients had undergone the first scan after a 24-hour period of octreotide withdrawal (28). Two studies showed unclear risk in the applicability concerns of patient selection because of the interindividual comparison design (30,32). Since the first and second scan results were measured independently, we graded the risk of bias and applicability concerns in both scans as low risk. Regarding the flow and timing, some studies had unclear risk because the time intervals between 2 scans were heterogeneous or they were interindividual studies (22,29,30,32,33).

Main findings of included studies

Table 3 provides an overview of the effect of SSAs treatment on radiolabeled SSAs uptake. The radiolabeled SSAs uptake decreased in the liver in patients after SSAs treatment in all studies (22-24,28,30-33). The same trend was also observed in the spleen in almost all studies, whereas only 1 study showed that the spleen-to-muscle ratio of ^{99m}Tc-hydrazinonicotinyl-Tyr3-octreotide (^{99m}Tc-HYNIC-TOC) did not significantly change following SSAs therapy (22,23,28,30,31,33). No convincing data revealed that SSAs treatment significantly changed the uptake of radiolabeled SSAs in the adrenal gland, kidney, pituitary gland, bone, and parotid gland. A total of 3 studies suggested that radiolabeled SSAs uptake might be decreased in the thyroid after SSAs treatment (22,23,31). Meanwhile, 8 studies evaluated the effect of SSAs treatment on tumor uptake of radiolabeled tracer, and among them, 3 showed increased tumor uptake after SSAs treatment whereas the remaining did not show any significant effect (22-24,28,30-33). In 5 studies, the tumor-to-liver/background ratio increased significantly after SSAs treatment (23,24,28,29,31).

Meta-analysis of SUVmax in normal organs and tumors

A total of 6 studies investigated the effect of SSAs on the uptake of the ^{68}Ga-labeled SSAs. Among these, 5 studies presented detailed data about the uptake of ^{68}Ga-DOTATATE in healthy organs and tumors. We further extracted and pooled these data and performed meta-analysis. *Figure 3* displays the pooled SUVmax prior to

Table 1 Characteristics of included studies in this systematic review and meta-analysis

First author	Year	Design	Comparison	Country	Patients	Age (years)	Clinical setting	SSA treatment	Uptake parameters	Time interval†	Time interval‡
Jahn (33)	2021	P	Intraindividual	Sweden	4	69±5.94	Small-intestinal NETs who were all progressing on long-acting SSA	Sandostatin LAR: 30 mg (1 patients) every 3 weeks; Sandostatin Autogel: 120 mg (2 patients) every 2 weeks, 120 mg (1 patients) every 4 weeks	SUV, normalized SUV, net uptake rate (Ki)	1–3.5 m	10–15 min
Gålne (24)	2019	P	Intraindividual	Sweden	19	65.7±8.2	Histologically verified NET with ongoing treatment with LA SSA, or evaluation of suspected NET with likely initiation of LA SSA treatment within a year	Lanreotide: 120 mg (9 patients) or 90 mg (2 patients) every 4 weeks Octreotide: 30 mg (4 patients) or 20 mg (4 patients) every 4 weeks	SUVmax (T/L)	202 d	14.7±8.8 d
Li (32)	2019	R	Interindividual	China	60	51.5	Patients with G2 NETs graded by 2010 WHO classification	Sandostatin LAR: 30 mg every 4 weeks	Target/ muscle ratio (T/M)	NA	14.7±8.0 d
Aalbersberg (23)	2019	P	Intraindividual	Netherland	34	64.2 [45–78]	Histologically confirmed well-differentiated NET (grade I–II)	Lanreotide: 60, 90, or 120 mg every 3–4 weeks for the individual patients	SUVmax, SUVmean, SUVpeak (T/L)	2 d	1 d
Cherk (31)	2018	R	Intraindividual	Australia	21	NA	Metastatic NETs	Sandostatin LAR: 30 mg (16 patients), 20 mg (2 patients) or 40 mg (1 patient) every 4 weeks Lanreotide: 90 mg or 120 mg (2 patients)	SUVmax (T/L)	2–12 m	3–4 w
Ayati (22)	2018	R	Intraindividual	Australia	30	64.6±13.4	Histologically-proven metastatic intermediately differentiated to well-differentiated NETs	Sandostatin LAR: 30 mg (29 patients) or 60 mg (1 patients) every 4 weeks	SUVmax, SUVmean	9.6 m	25.1±14.8 d
Haug (30)	2011	R	Interindividual + intraindividual	Germany	105	58±12	Histologically proven well- to intermediately-differentiated NET	Sandostatin LAR: 30 mg (33 patients), 20 mg (1 patients) or 50 mg (1 patient) every 4 weeks	SUVmax, SUVmean	NA	14.5±11.4 d

Table 1 (*continued*)

Table 1 (*continued*)

First author	Year	Design	Comparison	Country	Patients	Age (years)	Clinical setting	SSA treatment	Uptake parameters	Time interval[†]	Time interval[‡]
Janson (29)	1999	R	Intraindividual	Sweden	8	64 [49–74]	Five patients had malignant carcinoid tumors and three had malignant endocrine pancreatic tumors	Lanreotide: a daily dose of 6,000–12,000 μg four times daily	T/ background	10–13 m	3 d
Dörr (28)	1993	R	Intraindividual	Germany	5	NA	NETs midgut carcinoid with liver metastases and additional abdominal and/or mediastinal lymph node metastases	Octreotide: a daily dosage of 600 μg	T/ background	<4 w	<1 d

Data are presented as mean ± standard deviation or median [interquartile range]. [†], time interval between two scans; [‡], time interval between most recent SSA treatment and PET or SPECT scan. P, prospective; R, retrospective; NETs, neuroendocrine tumors; SSA, somatostatin analog; LA, long-acting; WHO, World Health Organization; LAR, long-acting release; SUV, standardized uptake value; SUVmax, maximum standardized uptake value; SUVmean, mean standardized uptake value; SUVpeak, peak standardized uptake value; T/L, tumor/liver; T/M, tumor/muscle; T, tumor; NA, not available; m, month; w, week; d, day; PET, positron emission tomography; SPECT, single photon emission computed tomography.

and after SSAs treatment in the liver (*Figure 3A*) and spleen (*Figure 3B*). The SUVmax of the liver prior to SSAs treatment was 9.56 (95% CI: 9.17–9.95, I^2=85.9%) and decreased to 7.62 (95% CI: 7.24–8.00, I^2=93.3%) following SSAs therapy. The corresponding parameters were 25.74 (95% CI: 24.61–26.88, I^2=77.9%) and 20.39 (95% CI: 19.29–21.49, I^2=80.3%) for spleen. As shown in Figure S1 and Figure S2, the summarized SUVmax of the adrenal gland, thyroid, and pituitary gland before SSAs treatment were 18.63 (95% CI: 17.68–19.58), 4.52 (95% CI: 4.10–4.95), and 3.99 (95% CI: 3.66–4.31), respectively. After SSAs treatment, the summarized parameters of these normal tissues were 17.81 (95% CI: 16.62–19.01), 3.03 (95% CI: 2.65–3.40), and 5.58 (95% CI: 4.83–6.33), respectively. SUVmax significantly decreased in the liver (P=0.001) and spleen (P=0.006) following SSAs treatment whereas no significant change was noted in the adrenal gland (P=0.83), thyroid (P=0.07), and pituitary gland (P=0.33) (*Figure 4A*). With regard to tumor uptake, pooled parameters before and after SSAs treatment are demonstrated in Figure S3 and Figure S4. The uptake of the hottest lesion did not differ significantly between pre-and post-treatment scans (28.14±14.3 *vs.* 29.28±14.51, P=0.37). In addition, neither primary tumor sites nor metastases showed significant differences after SSAs treatment (*Figure 4B*).

Discussion

This meta-analysis summarizes the effect of SSAs therapy prior to imaging on the uptake of radiolabeled SSAs for NETs patients. We detected significantly decreased tracer uptake in the liver and spleen after SSAs treatment, especially uptake of ^{68}Ga-labeled SSAs. Conversely, no significant change was observed in primary tumor sites or metastatic lesions.

SSAs, as synthetic SSAs targeting SSTRs, have been widely applied in NETs imaging and therapy (34). The rationale is the tumor cell receptor-mediated internalization of the radio- or non-radiolabeled SSAs and their retention in the cytoplasm (21). Theoretically, treatment with nonradioactive SSAs could result in possible SSTRs occupancy and blockade, and then interfere with the interpretation of radiolabeled SSAs imaging. Velikyan *et al.* found that different doses of octreotide (0, 50, 250, and 500 μg) administered immediately before ^{68}Ga-DOTATOC PET/CT imaging affected the ^{68}Ga-DOTATOC uptake, revealing a blocking or saturation effect at higher amounts of SSA (35). Thus, current SSTRs imaging guidelines

Table 2 Information on PET/CT or SPECT scanning in this systematic review and meta-analysis

First author	Year	Modality	Ligand	Dose (MBq)
Jahn (33)	2021	Discovery MI, GE Healthcare	^{68}Ga-DOTATOC	167±21
Gålne (24)	2019	Discovery 690 scanner (GE Healthcare)	^{68}Ga-DOTATATE	2.5 MBq/kg
Li (32)	2019	Discovery NM/CT 670, GE	^{99m}Tc-HYNIC-TOC	370
Aalbersberg (23)	2019	Gemini TOF PET/CT (Philips)	^{68}Ga-DOTATATE	100
Cherk (31)	2018	Discovery 690 GE Healthcare or Siemens Biograph Healthcare	^{68}Ga-DOTATATE	85–307
Ayati (22)	2018	Gemini TOF PET/CT scanner (Philips)	^{68}Ga-DOTATATE	110–185
Haug (30)	2011	Gemini PET/CT scanner (Philips)	^{68}Ga-DOTATATE	200
Janson (29)	1999	SPECT (Nuclear Diagnostics, Hagersten, Sweden and London, UK)	^{111}In-pentetreotide	144 [114–238]
Dörr (28)	1993	Siemens Orbiter 7500 Gamma Camera	^{111}In-pentetreotide	137 [105–237]

Data are presented as mean ± standard deviation, median [interquartile range] or n. PET/CT, positron emission tomography/computed tomography; SPECT, single photon emission computed tomography; MI, molecular imaging; NM, nuclear medicine; TOF, time of flight; ^{68}Ga, Gallium-68; ^{99m}Tc, Technetinum-99m; ^{111}In, Indium-111.

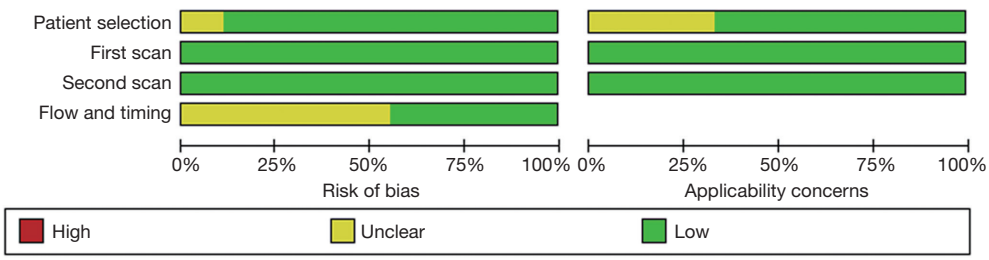

Figure 2 Quality assessment of diagnostic studies-2 revision evaluation of the risk of bias and applicability concerns among the 9 studies.

recommended the discontinuation of SSAs therapy prior to imaging to avoid possible decreased radioactive SSAs uptake (15). However, most of our included studies reported inconsistent results, of which 3 studies showed a significant increase in tumor lesions after SSAs treatment, whereas in 5 studies, the difference of tumor uptake was not significant. Taken together, our pooled results indicate that SUVmax of primary tumors or metastases did not change significantly after SSAs treatment. The plausible explanation may be the fast SSTRs recovery in NETs within a short time frame, compared to that in normal organs (36,37). Although our findings may represent the worst-case scenario, they may indicate that nonradioactive SSAs treatment has little effect on the tumor uptake of radiolabeled SSAs on SSTRs imaging.

In contrast to the change of tumor uptake after SSAs, our results showed that the SUVmax of ^{68}Ga-labeled tracer in the liver and spleen were significantly decreased on the posttreatment scan with an approximately 20% reduction, whereas no significant difference was observed in other normal tissues including the adrenal, thyroid, and pituitary glands. These findings are almost in agreement with previously reported relevant studies. In a prospective study with intraindividual design, Aalbersberg *et al.* reported significantly decreased SUVmax in the liver (10.15 *vs.* 9.08, P<0.001) and spleen (25.77 *vs.* 22.35, P<0.001) after SSAs, with a reduction of about 10% (23). A recent study showed a higher reduction of 25% and 20% in physiologic spleen and liver accumulation, respectively, similar to our findings (23). It should be noted that following SSAs therapy, the thyroid uptake also decreased although the difference did not reach statistical significance due to the small sample size. Some studies also investigated the uptake difference in the kidney, parotid gland, and bone between 2 PET/CT scans, but these data were too scarce to be pooled in this meta-analysis. The different tendency between tumor and liver or spleen uptake may be due to different SSTRs recycling kinetics mainly consisting of receptor internalization and expression

Table 3 Overview of tracer uptake in normal tissues and tumor lesions before and after SSAs treatment

Author [year]	Liver	Spleen	Kidney	Adrenal gland	Thyroid	Pituitary gland	Parotid gland	Bone	Tumor	Tumor-to-liver/background ratio
Jahn [2021][†] (33)	↓	↓	NS	–	–	–	–	NS	NS	–
Gålne [2019] (24)	↓	–	–	–	–	–	–	–	NS	The tumor-to-liver ratio was higher after treatment initiation with LA SSA and the tumor lesions in the liver were better visualized
Li [2019][‡] (32)	↓	NS	NS	NS	–	–	–	↓	NS	–
Aalbersberg [2019] (23)	↓	↓	NS	NS	↓	NS	NS	NS	↑	The tumor-to-liver ratio for SUVmax increased after lanreotide injection in all lesions
Cherk [2018] (31)	↓	↓	–	NS	↓	↑	NS	–	↑[§]	Metastatic lesion uptake and lesion-to-liver SUVmax ratio increased in 82% of lesions following SSA therapy
Ayati [2018] (22)	↓	↓	–	NS	↓	NS	–	–	NS	–
Haug [2011] (30)	↓	↓	NS	NS	–	NS	–	–	NS	–
Janson [1999] (29)	–	–	–	–	–	–	–	–	–	The tumor-to-background ratio had an average increase in the ratio of 50%, while the spleen-to-background ratio decreased significantly (the average reduction ratio was 55%)
Dörr [1993] (28)	↓	↓	↓	–	–	–	–	–	↑	The tumor-to-liver ratio improved markedly

[†], the time interval was 7 hours; [‡], the individual measurement of tracer uptake was target-to-muscle ratio; [§], 61% of metastatic lesions had an increase in SUVmax following SSA therapy. ↓, decrease; ↑, increase; –, not available; SSAs, somatostatin analogs; NS, no significance; SUVmax, maximum standardized uptake value.

after SSAs therapy (37). Interestingly, a recent study that investigated the time-dependent extended effect of SSAs on the tumor versus normal tissue uptake of ^{68}Ga-DOTATOC found that tumor SUV decreased significantly from baseline to 1 hour post-injection but subsequently increased to baseline level at 4 hours whereas the uptake in the liver and spleen remained significantly below baseline level at 7 hours, suggesting faster SSTRs recycling in tumors than in normal tissues (33). In addition, the difference in inherent receptor density could also lead to the different thresholds for receptor saturation in normal tissues and tumors (38,39).

Given that there was no evidence of decreased tumor uptake but significant reduction in the liver or spleen uptake, several included studies consistently demonstrated the improved tumor-to-liver or background ratio after SSAs treatment. In spite of the prominent heterogeneity of NETs, this finding may be generalized to all types of this tumor. Aalbersberg *et al.* reported increased tumor-to-liver ratio for SUVmax in all lesions after SSA, including abdominal, liver, lymph node, and bone lesions (23). The increased ratio not only facilitates tumor detection but also provides obvious implications for peptide receptor radionuclide treatment (PRRT). Firstly, the improved tumor-to-background or liver ratio perhaps increases the likelihood of being suitable for PRRT. Then, nonradioactive SSAs pretreatment may decrease the uptake of ^{177}Lu- or ^{90}Y-SSAs in normal tissues, especially in the spleen, thus reducing potential radiation exposure and adverse side effects on normal tissues (40). However, the amount of peptide administered during PRRT is much higher than that for ^{68}Ga-SSAs PET/CT, thus further research is needed to confirm our findings in PRRT (39). Apart from these, the change in tumor-to-

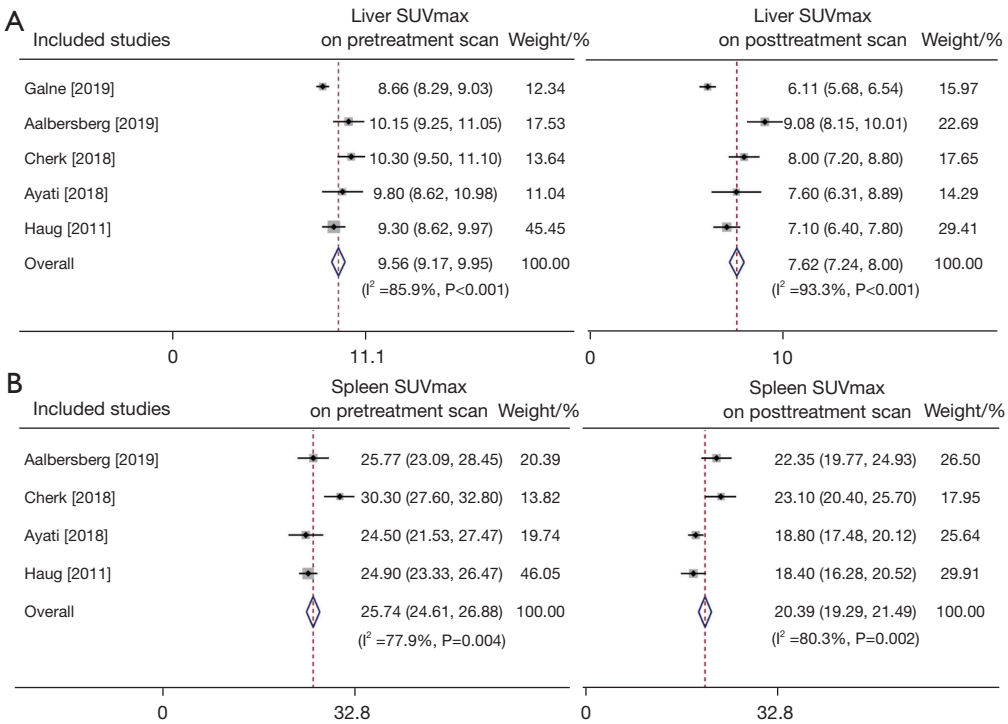

Figure 3 Forest plots of SUVmax before and after SSAs treatment. (A) SUVmax in the liver. (B) SUVmax in the spleen. SUVmax, maximum standardized uptake value.

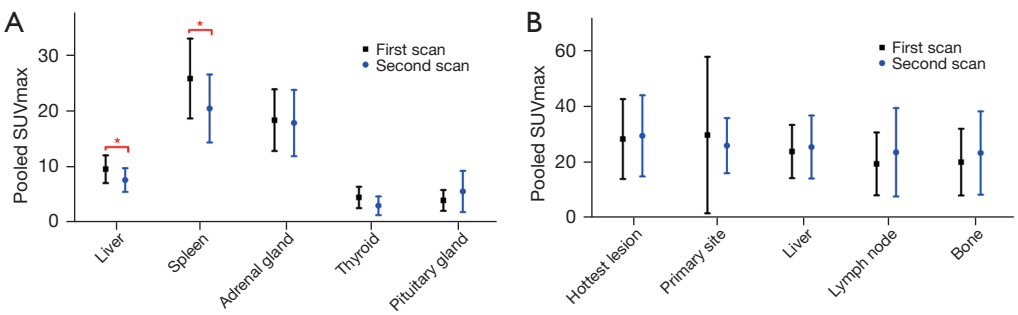

Figure 4 Pooled SUVmax change between the first and second scan. (A) SUVmax change in normal tissues. (B) SUVmax change in tumor lesions. Plots indicate the pooled SUVmax with 95% confidence intervals. *, statistical significance. SUVmax, maximum standardized uptake value.

liver or -spleen ratio was also used as a valid marker for evaluating the disease status in some studies (41-43). Clinicians should be aware of the effect of SSAs on the tumor-to-background ratio on SSTRs imaging, in case of misdiagnosis as disease progression during response assessment.

Consistent with previous studies, our systematic review and meta-analysis that supports no withdrawal of SSAs treatment prior to SSTRs imaging might affect the procedure guideline for ^{68}Ga-DOTA-SSAs PET/CT. If continuation of SSAs treatment prior to SSTRs imaging is undertaken, it is of great benefit to patients by controlling the symptoms and reducing the risk of tumor growth. There is also no need for patients to use short-acting SSAs instead that has to be administrated 3 times daily for preparation of SSTRs imaging. Meanwhile, the nuclear medicine

Table 4 Implications for PET interpretation according to the current meta-analysis

Items	Guideline	Our findings
SSAs preparation before the scan	Withdrawal for 3–4 weeks or 4–6 weeks[†]	No withdrawal[†]
	1–2 days[‡]	Withdrawal for several hours (>4 hours)[‡]
Implications for PET interpretation	No decreased uptake in tumor sites whereas decreased uptake in healthy organs (e.g., liver, spleen)	
	Cautious about using tumor-to-liver/spleen ratio for response assessment	

[†], long-acting SSAs; [‡], short-acting SSAs. PET, positron emission tomography; SSAs, somatostatin analogs.

department can have flexible schedules for SSTRs imaging without having to adhere to the SSAs administration time.

Our study has some limitations. Firstly, the number of included articles was relatively small, especially for pooled analysis, which might be a possible source of bias. Secondly, prominent heterogeneity of the study design was found among included studies, such as SSAs treatment, time intervals between 2 scans, and from the last injection to posttreatment scan, which significantly affected the reliability of pooled results. In addition, the study quality including patient selection, various radiolabeled SSAs, and diverse imaging outcomes also made contributions to the high heterogeneity. Thirdly, the included studies used different radiolabeled SSAs tracers, scanners, and scanning methods, thus the imaging interpretation and parameter measurement may be inconsistent among studies.

Conclusions

SSAs therapy prior to imaging resulted in a significant reduction in the liver and spleen uptake, but did not decrease the uptake of radiolabeled SSAs in tumor primary or metastatic sites as well as other normal tissues. These findings have significant implications for procedure guidelines of SSTRs imaging and support the unnecessary discontinuation of SSAs prior to radiolabeled SSAs imaging (*Table 4*). Further prospective, multicenter, and long-term prospective longitudinal studies with a large sample are also needed to better determine the effect of SSAs therapy on the uptake of radiolabeled SSAs in normal organs and tumor lesions.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Quality Assessment of Diagnostic Accuracy Studies-2 revision

Domain	Patient selection	First scan	Second scan	Flow and timing
Description	Describe methods of patient selection	Describe the first scan and how it was conducted and interpreted	Describe the second scan and how it was conducted and interpreted	Describe any patients who did not receive the first scan and/or the second scan (refer to flow diagram)
	Describe included patients (presentation, intended use of 2 scans, and setting)			Describe the time interval and any interventions between the first scan and second scan
Signaling questions (yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Were the first scan results interpreted without knowledge of the results of the second scan?	Is the second scan likely to correctly classify the target condition?	Was there an appropriate interval between the first scan and second scan?
	Was a case-control design avoided?		Were the second scan results interpreted without knowledge of the results of the first scan?	Did all patients receive both scans?
	Did the study avoid inappropriate exclusions?			Were all patients included in the analysis?
Risk of bias (high, low, or unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the first scan have introduced bias?	Could the second scan, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability: yes/no/unclear	Are there concerns that the included patients do not match the review question?	Are there concerns that the first scan, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the second scan does not match the review question?	–

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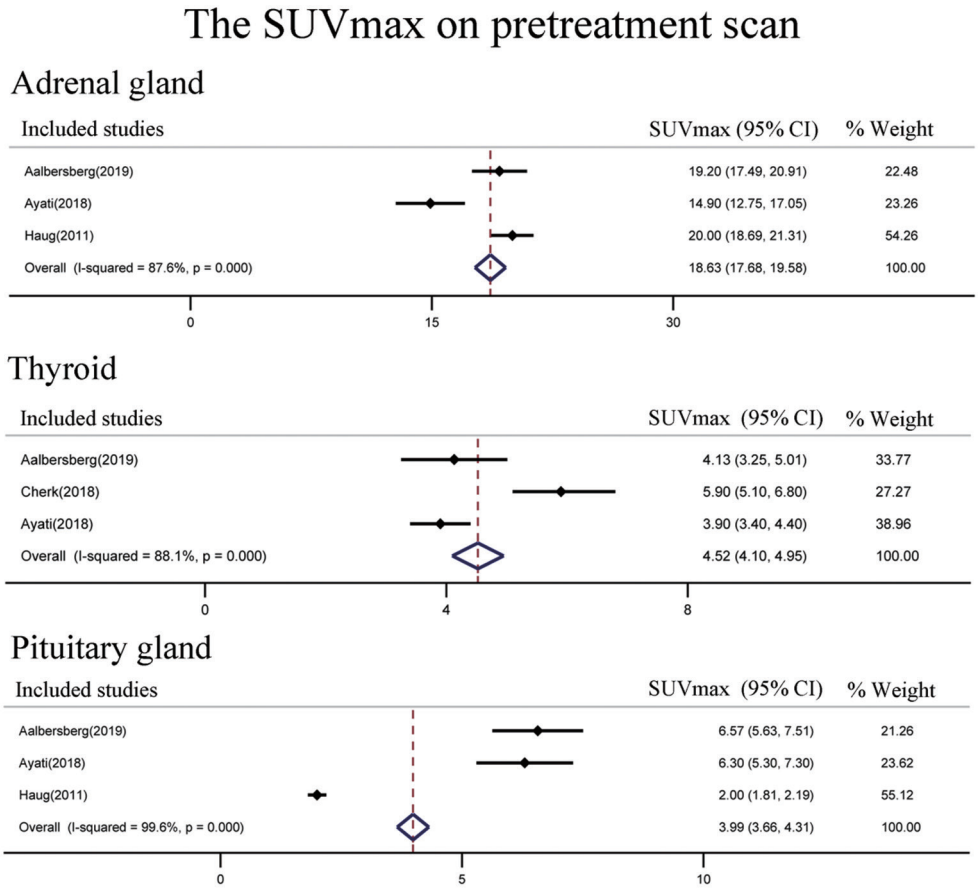

Figure S1 Forest plots of SUVmax in the adrenal gland, thyroid, and pituitary gland before SSAs treatment. SUVmax, maximum standardized uptake value; CI, confidence interval; SSAs, somatostatin analogs.

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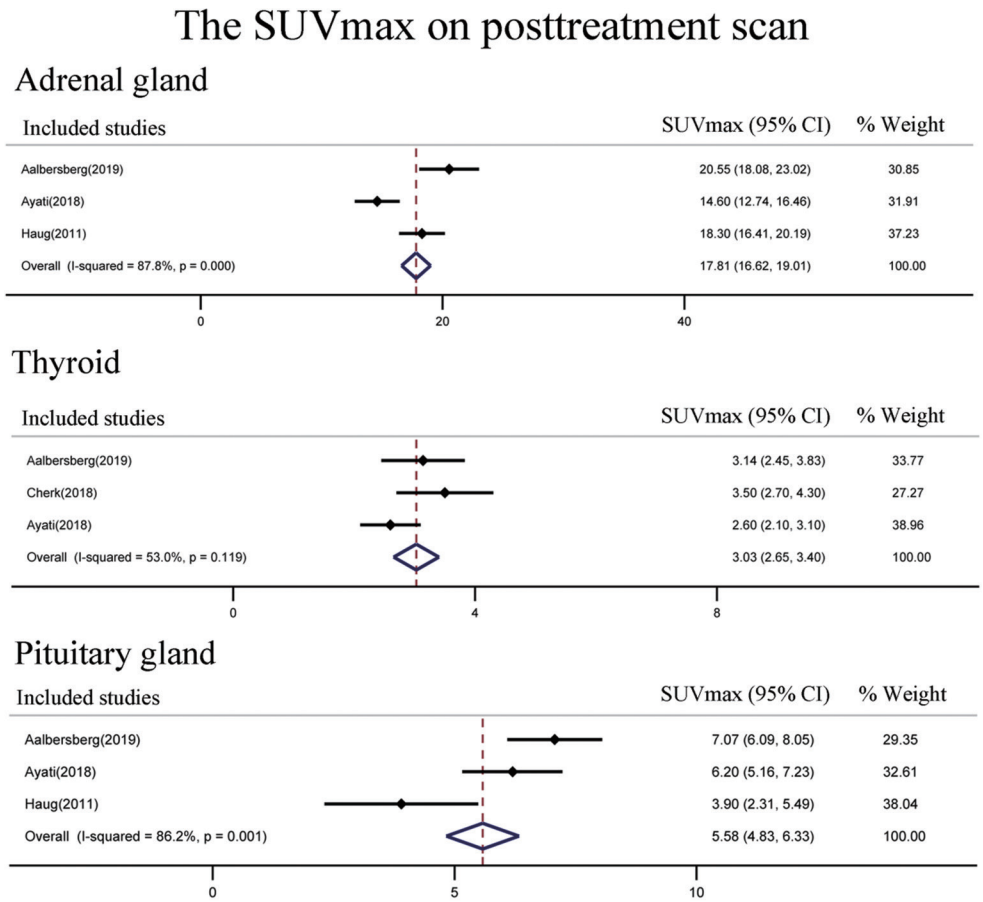

Figure S2 Forest plots of SUVmax in the adrenal gland, thyroid, and pituitary gland after SSAs treatment. SUVmax, maximum standardized uptake value; CI, confidence interval; SSAs, somatostatin analogs.

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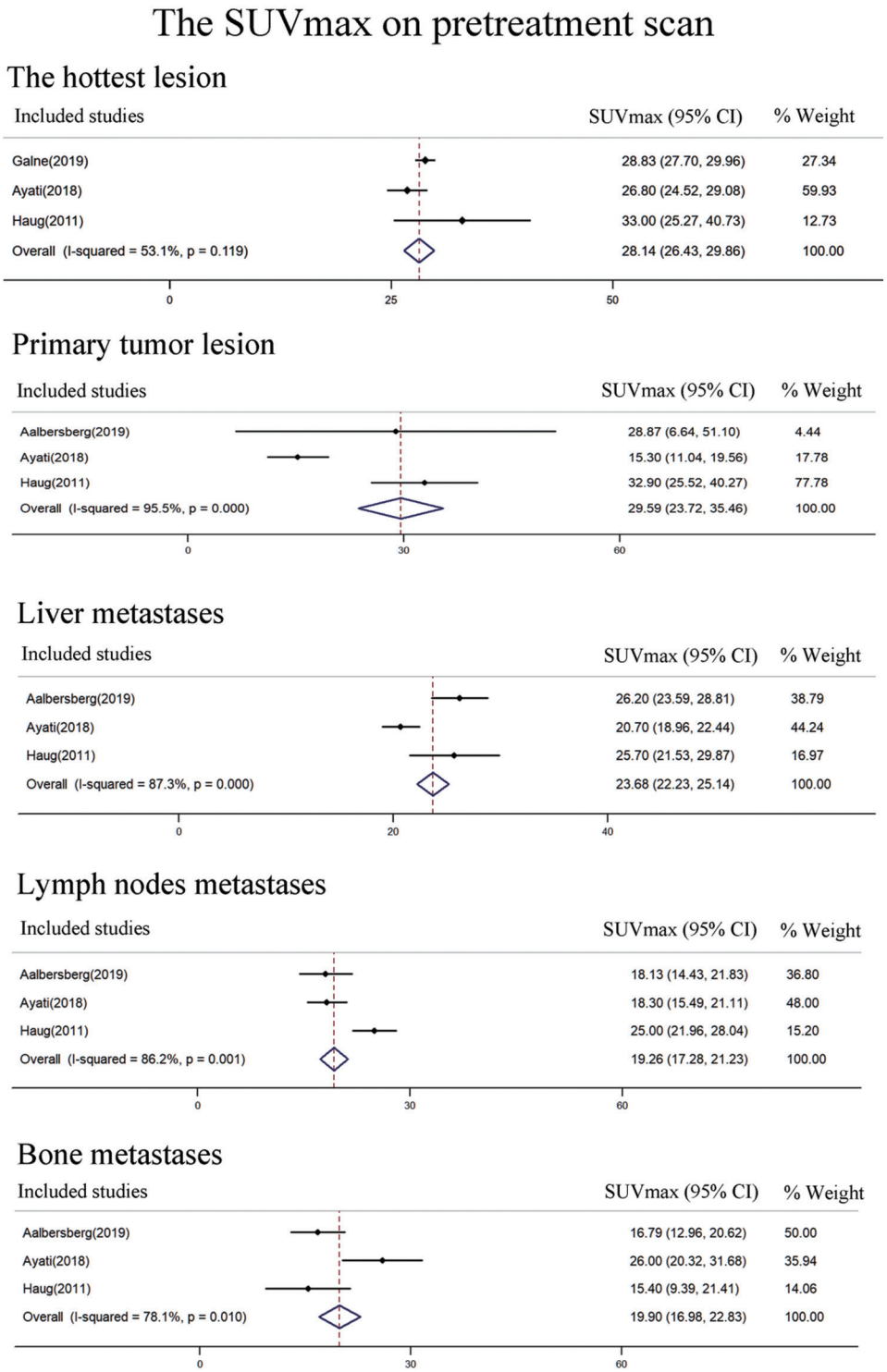

Figure S3 Forest plots of SUVmax in tumor lesions before SSAs treatment. SUVmax, maximum standardized uptake value; CI, confidence interval; SSAs, somatostatin analogs.

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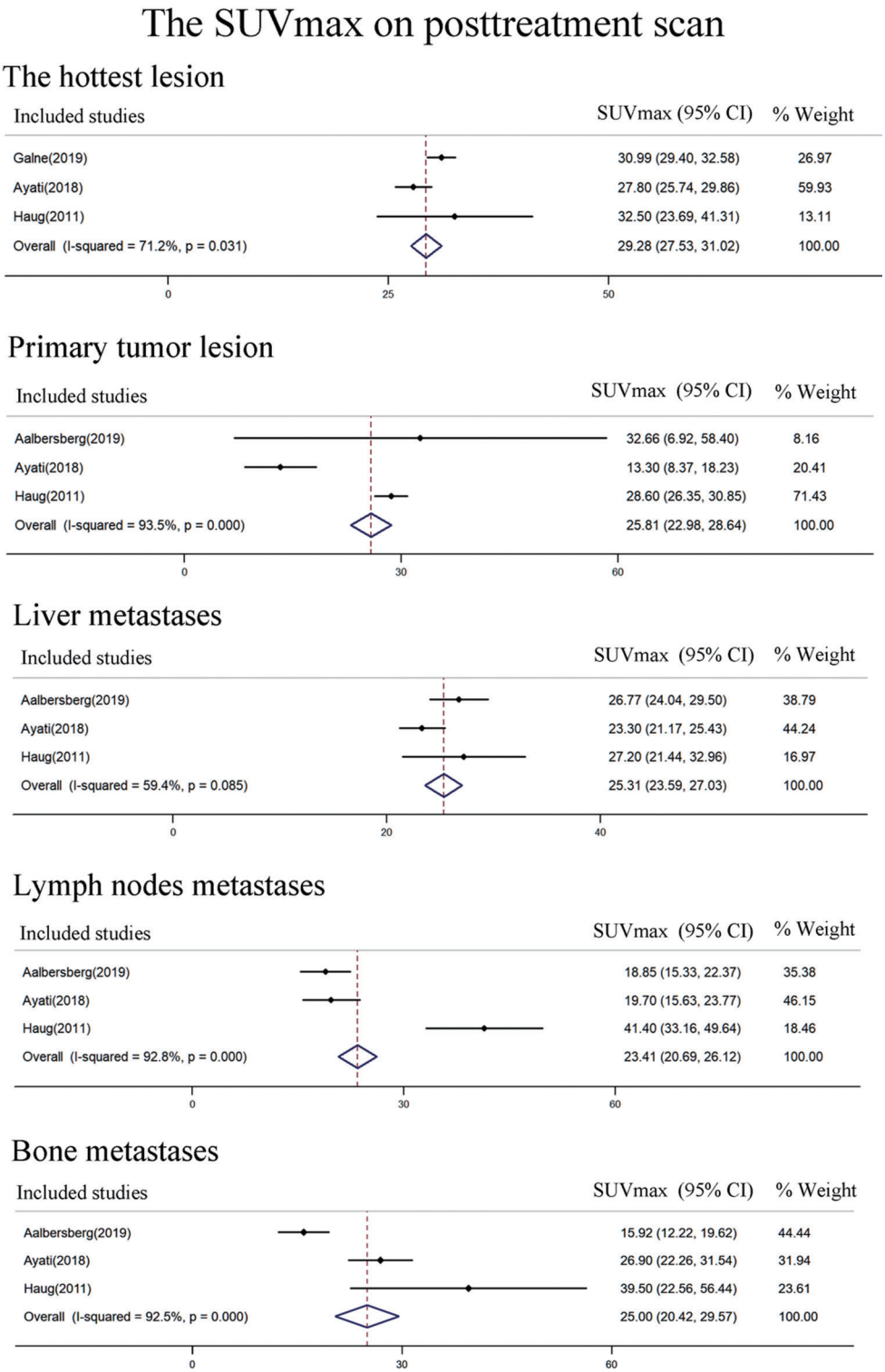

Figure S4 Forest plots of SUVmax in tumor lesions after SSAs treatment. SUVmax, maximum standardized uptake value; CI, confidence interval; SSAs, somatostatin analogs.

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