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# Impact of Cold Somatostatin Analog Administration on Somatostatin Receptor Imaging

## *A Systematic Review*

*David Morland, MD, PhD,*†‡§ Nicolas Laures, MD,||¶ Elizabeth Katherine Anna Triumbari, MD,* Marine Perrier, MD,||¶ Alessio Imperiale, MD, PhD,** Salvatore Annunziata, MD, PhD,* and Vittoria Rufini, MD, PhD††‡‡§§*



**Purpose:** The interactions between the administration of cold somatostatin analogs (cSAs) and their radiolabeled counterpart remain unclear, and discontinuation before imaging is still advised as a precaution. The aim of this systematic review is to evaluate the consequences of cSA administration on tumoral and surrounding healthy organs' uptake at somatostatin receptor (SSTR) imaging with SPECT or PET.

**Methods:** After registration of the study on Prospero (CRD42022360260), an electronic search of PubMed and Scopus databases was performed. Inclusion criteria were as follows: human patients referred for SSTR imaging for oncological purposes; at least 1 examination performed either before cSA administration or after a long-enough withdrawal of cSA treatment; at least 1 examination was performed under cSA treatment. Included articles were independently appraised by 2 authors using the standardized protocol provided by the Quality Assessment of Diagnostic Accuracy Studies. Discrepancies were solved by consensus.

**Results:** A total of 12 articles were included, 4 using $^{111}$In-pentetreotide and 8 using $^{68}$Ga-DOTA peptides. Administration of cSAs consistently resulted in decreased spleen and liver uptake (from 6.9% to 80% for spleen, 10% to 60% for liver) and increased tumor-to-background or tumor–to–healthy organ ratios. After cSA treatment, tumor uptake alone was unchanged or moderately decreased. Similar results were noted whether patient was octreotide-naive.

**Conclusion:** Impairment in SSTR imaging quality after cSA administration has not been demonstrated. On the contrary, the administration of cSAs seems to improve the contrast between tumoral lesions and the surroundings.

**Key Words:** contrast, neuroendocrine, PET, somatostatin, SPECT

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From the *Unità di Medicina Nucleare, GSTeP Radiofarmacia, TracerGLab, Dipartimento di Radiologia, Radioterapia ed Ematologia, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy; †Médecine Nucléaire, Institut Godinot; ‡CReSTIC, EA 3804; §Laboratoire de Biophysique, UFR de Médecine, Université de Reims Champagne-Ardenne; ||Hépato-Gastro-Entérologie et Cancérologie Digestive; ¶Unité de Médecine Ambulatoire—Cancérologie Hématologie, CHU de Reims, Reims; **Médecine Nucléaire, Institut de Cancérologie de Strasbourg Europe, Université de Strasbourg, Strasbourg, France; ††Unità di Medicina Nucleare, Dipartimento di Radiologia, Radioterapia ed Ematologia, Fondazione Policlinico Universitario A. Gemelli, IRCCS; ‡‡Istituto di Medicina Nucleare, Dipartimento di Radiologia, Radioterapia ed Ematologia, Università Cattolica del Sacro Cuore; and §§ENETS Center of Excellence for the Diagnosis and Cure of Neuroendocrine Tumors, Rome, Italy.

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Correspondence to: David Morland, MD, PhD, Médecine Nucléaire, Institut Godinot, 1 rue du général Koenig 51100 Reims, France. E-mail: david.morland@reims.unicancer.fr.



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Somatostatin receptor (SSTR) imaging currently plays a central role in the management of several types of tumors, first and foremost neuroendocrine tumors (NETs).[1] Initially confined to single-photon emitting radiopharmaceuticals with $^{111}$In-pentetreotide, SSTR imaging possibilities have been extended to positron emitters with the arrival of $^{68}$gallium-labeled peptides, notably $^{68}$Ga-DOTATATE and $^{68}$Ga-DOTATOC.

The benefit of treatment with cold somatostatin analogs (cSAs) is widely demonstrated in NETs,[2] both for secretory syndrome and tumor control. Initially limited to short-acting release (SAR) formulations, long-acting release (LAR) cSA formulations have made their appearance.[2] The interactions between cSAs, whether SAR or LAR, and their radiolabeled counterpart remain unclear.[3] To date, in the hypothesis of a competitive action on SSTRs between the two, a discontinuation of cSAs before SSTR imaging has been advised, most often based on a precautionary principle. The European Association of Nuclear Medicine procedure guidelines recommend a time interval of 3 to 4 weeks after administration of LAR cSAs before performing PET/CT, meanwhile acknowledging that the effects of cSAs therapy have not been well characterized.[4]

The aim of this systematic review was to gather information from the literature to evaluate the true consequences of cSA administration on tumor uptake as well as on healthy organs' uptake, based on within-patient data.

## METHODS

### Research Strategy

This systematic review was performed according to the standards of the PRISMA-P statement and was registered on the Prospero Web site (registration code: CRD42022360260). An electronic search of PubMed and Scopus databases was independently performed by 2 authors (D.M. and N.L.) to identify articles evaluating the impact of cSA administration on SSTR imaging. The search strategy was built using the following search string (Equation 1) and was last updated on September 6, 2022:

$$(\text{Scintigraphy OR PET}) \text{ AND } (\text{somatostatin OR SSTR OR SST}) \text{ AND } (\text{cold OR octreotide OR lanreotide}) \quad (1)$$

### Screening and Inclusion and Exclusion Criteria

First, duplicate findings between PubMed and Scopus were automatically removed through the functions available in the reference manager used (JabRef, JabRef Bibliography Management). The remaining articles were screened for eligibility, based on title and abstract.

Inclusion criteria were as follows: (i) human patients referred for SSTR imaging for oncological purposes; (ii) at least 1 examination

performed either before cSA administration or after a long-enough withdrawal of cSA treatment (>24 hours for subcutaneous formulations; imaging performed the week before the next administration, for long-acting formulations); (iii) at least 1 examination performed under cSA treatment; (iv) available quantitative or semiquantitative data on the uptake of healthy organs or tumoral lesions; (v) intrapatient comparison (percentage of decrease/increase in the measures on the same patients); and (vi) written in the first language of at least 2 of the authors of this review (English, French, or Italian). Exclusion criteria were as follows: (i) diseases other than cancer; and (ii) reviews, expert opinions, comments, letters to the editor, case reports, studies on animals, and conference reports.

Full texts of the potentially eligible studies were retrieved for further evaluation. A cross-reference check was also performed to identify any additional studies to be included.



## Quality Assessment

Two authors (D.M. and N.L.) independently assessed the methodological quality of the included articles using the standardized protocol provided by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2). Any disagreement was solved by consensus. The QUADAS-2 scores of its 4 key domains (patient selection, index test, reference standard, flow and timing), evaluated with regard to the risk of bias and methodological applicability, were recorded and tabulated for all included studies, and a summary report was constructed. Studies with a low risk of bias for all items or not more than 1 item evaluated with uncertain risk were deemed of sufficient quality for final inclusion.

## Data Collection

An Excel review database was generated. The following parameters were extracted from each article: year of publication, first author, number of patients in the subgroup of interest, cancer type, administered radiotracer (name, activity, peptide mass), first imaging session data (patient's preparation regarding cSAs, acquisition protocol), delay between first and second imaging sessions, cSAs data (name, administration protocol, last administration before radiotracer administration during the second imaging session), ratio between cold and hot somatostatin analog; second imaging session acquisition protocol; quantitative/semiquantitative measures (% of decrease, evolution of absolute $SUV_{max}$ values) for healthy organs (spleen, liver, kidneys, adrenals, pituitary, thyroid, bone marrow, pancreas), and tumoral lesions. This database was independently filled in by 2 authors (D.M. and N.L.), and discrepancies were solved by consensus.

# RESULTS

This systematic literature search initially yielded a total of 3706 articles (PubMed: 1774 articles; Scopus: 1932 articles). Once the 1165 duplicates were excluded, 2541 articles were screened based on their title and abstract. Of these, 20 full texts were sought for retrieval. Eight articles were further excluded: 1 did not have an available manuscript, 1 was a duplicate, and 6 did not have any within-patient comparison. Finally, 12 articles were included in the study[3,5–15] (Fig. 1). All studies were deemed of sufficient methodological quality based on QUADAS-2 assessment (Table 1). All articles rely on the same design, with a baseline imaging (without administration of cSAs or after a sufficiently long period of withdrawal of a long-term treatment, later referred as "imaging session 1") and a second imaging session under cSA treatment (later referred as "imaging session 2"). One article included patients with small cell lung cancer (SCLC); the other 11 articles included patients with NETs. Studies' design and results are presented in Table 2 and Table 3.

## Octreotide-Naive Patients Before Baseline Imaging (Imaging Session 1)

### Start of Short-Acting Octreotide Treatment Immediately Before Imaging Session 2

Two prospective studies fall into this category: one published by Velikyan et al[9] in 2010 and a second proposed by Lodge et al[3] in 2021.

In the study by Velikyan et al,[9] a subgroup of 6 patients underwent sequential $^{68}$Ga-DOTATOC PET/CT examinations preceded by the administration of 0 (baseline, image 1), 50 (image 2), and 250 or 500 μg of octreotide (high dosage, image 3) 10 minutes before tracer administration. A 3-hour interval between the examinations was observed, and each PET/CT was performed 50 minutes after radiopharmaceutical administration. Injected $^{68}$Ga-DOTATOC activities ranged from 15 (image 1) to 80 MBq (images 2 and 3). In 4 of 5 patients, for which liver values were available, the lesion-to-liver ratio increased from baseline to the 50-μg pretreated scan (average increase ranging from 13% to 108%). From baseline to the last study, the lesion-to-liver ratio also increased with an average of 88% (range, 1%–223%). Liver and spleen uptake decreased after 50-μg and high-dosage octreotide pretreatment (at least −20% and −40%, respectively, based on the reported figure at high dosage). Kidney uptake only decreased after high cold octreotide pretreatment.

Lodge et al[3] published a prospective study including 7 patients who underwent 2 $^{68}$Ga-DOTATOC PET/CT scans: the first without cold octreotide and the other with the administration of 50 μg of short-acting octreotide 10 to 15 minutes before radiotracer administration. The 2 examinations were performed less than 21 days from each other (1–20 days). Spleen uptake and liver uptake were significantly decreased on the second PET/CT (−48% and −27%, respectively) with images performed 60 minutes after radiotracer administration. No significant difference was noted for other healthy organs or tumor's uptake.

### Start of Short-Acting Octreotide Treatment Less Than 2 Weeks Before Imaging Session 2

In 1997, Soresi et al[6] published a prospective study including 12 patients with SCLC. Two scans were performed, both 5 hours after the administration of 110 to 130 MBq of $^{111}$In-pentetreotide: a first one without any treatment and a second one after a 7-day treatment of short-acting octreotide (600 μg/d). Tumor-to-lung and tumor-to-liver ratios increased at imaging session 2 (1.98 vs 1.83 and 0.78 vs 0.67, respectively).

### Long-term Octreotide Treatment Started Before Imaging Session 2

Six studies allow intrapatient comparisons before and after initiation of long-term (between 2 and 13 months) octreotide treatment.

The 2 oldest studies[7,8] used $^{111}$In-pentetreotide scintigraphy. Janson et al[7] compared spleen-to-background and tumor-to-background ratios of 8 patients after 10 to 13 months of lanreotide treatment. The spleen-to-background ratio was reduced by 55%, and the tumor-to-background ratio was increased by 50% (range, −79% to 1087%). A similar study was conducted by Rolleman et al[8]: 2 scans were performed 50 to 397 days from each other: a significant decrease in spleen uptake was noted (−69%). A nonsignificant decrease in liver, kidney, and tumoral uptake was also observed.

The remaining 4 studies used $^{68}$Ga-DOTATATE PET/CT and LAR cSAs. Intrapatient analysis was possible for a subgroup in the study by Haug et al[10] (9 patients), a subgroup in the study by Gålne et al[14] (19 patients), and the entire population of the other 2 studies (30 patients and 34 patients, respectively).[11,13] Tumor uptake was not significantly altered by the pretreatment

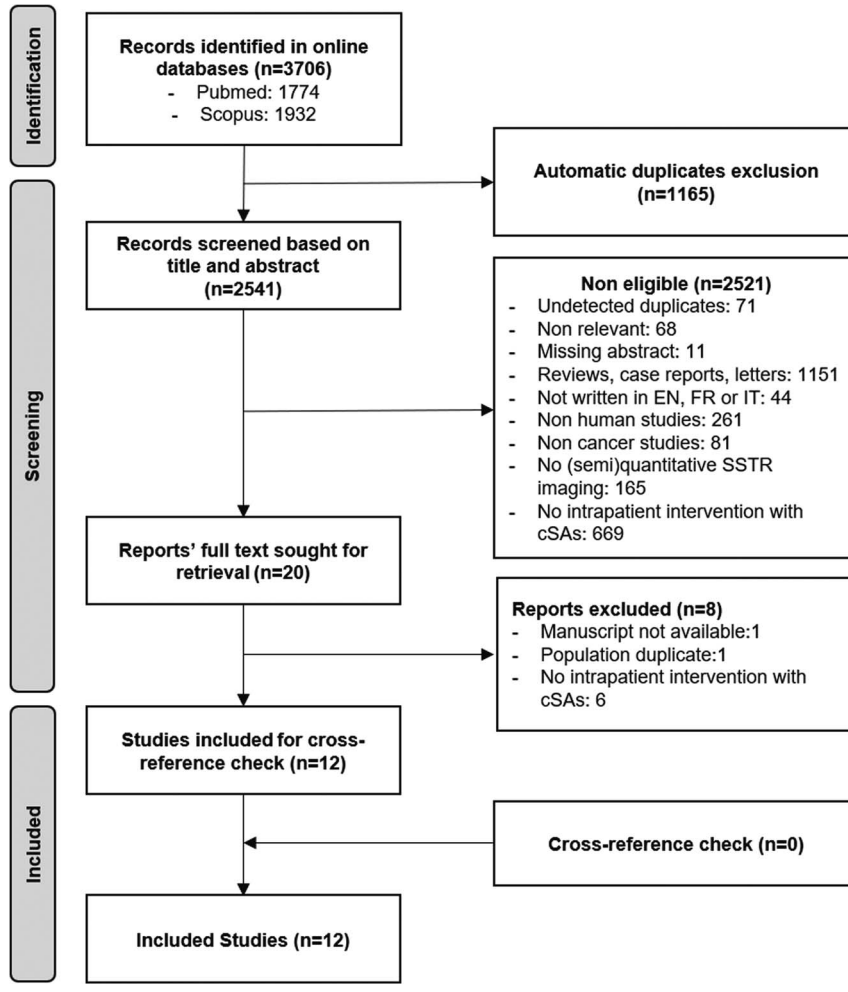


**FIGURE 1.** Systematic review flowchart. EN, English; FR, French; IT, Italian.

with cSAs, differently from tumor–to–healthy organ ratios, which were found increased.[14] The liver uptake was systematically decreased under cSAs.

## Patients Under Long-term Octreotide Treatment Before Baseline Imaging

Aalbersberg et al[12] prospectively studied the effect of cSAs on $^{68}$Ga-DOTATATE uptake, 1 day before and 1 day after injection of lanreotide in 34 patients whose treatment had been initiated at least 4 months earlier. The tumor-to-liver ratio increased moderately but significantly on day +1 of the analogs (2.59 vs 2.21); liver, spleen, and thyroid uptake decreased significantly.

Jahn et al[15] studied the effect of 400-µg octreotide administration at 15 minutes before $^{68}$Ga-DOTATOC in 4 patients already treated with LAR cSAs. Three whole-body acquisitions were performed (1, 4, and 7 hours) and compared with a baseline acquisition performed 1 to 3.5 months before. Tumor SUV values decreased significantly from baseline to 1 hour after injection, but subsequently increased over time and became similar to baseline at 4 and 7 hours. The uptake in liver, spleen, and pancreas remained significantly below baseline levels.

## Other Studies

The oldest study[5] included in our review prospectively gathered 5 patients (2 octreotide-naive patients and 3 patients who withdrew short-acting octreotide 24 hours before imaging). Two sessions of 3 scans (planar acquisitions 0.5, 4, and 24 hours after 105–237 MBq of $^{111}$In-pentetreotide) were performed without and with octreotide (600 µg/d) within 28 days from each other. Healthy organs concentrated less tracer under treatment (at 4 hours: −60% for the spleen, −28% for the liver, and −17% for the kidneys), whereas the tumor-to-liver ratio increased (>20%).

## Peptide Mass, Cold-to-Radiolabeled Ratio

The administered radiolabeled peptide mass was not available in all studies. In the absence of further pharmacokinetic studies with LAR cSAs, the cold-to-radiolabeled ratio was only calculable with SAR cSAs and encompassed at least the range from 33:1 (50 µg of cold peptide for 1.5 µg of radiolabeled peptide[9]) to 100:1 (500 µg of cold peptide for 4.95 µg of radiolabeled peptide[9]).

# DISCUSSION

## Effect of cSAs on Healthy Organs' Uptake

Administration of cSAs consistently resulted in decreased spleen and liver uptake. A total of 10 studies explicitly reported splenic uptake: 9 described a significant decrease and 1 a nonsignificant decrease. The magnitude of the decrease varied between 6.9% and 80%. A similar phenomenon was observed for the liver: 10 studies reported hepatic uptake, 9 of which with a significant

**TABLE 1.** QUADAS-2 Assessment of Included Studies

| | Patient Selection | | Index Test | | Reference Standard | | Flow and Timing |
|---|---|---|---|---|---|---|---|
| **Author (Year)** | **Risk of Bias** | **Applicability Concerns** | **Risk of Bias** | **Applicability Concerns** | **Risk of Bias** | **Applicability Concerns** | **Risk of Bias** |
| Dörr et al (1993)[5] | Unclear | Low | Low | Low | Low | Low | Low |
| Soresi et al (1997)[6] | Unclear | Low | Low | Low | Low | Low | Low |
| Janson et al (1999)[7] | Low | Low | Low | Low | Low | Low | Low |
| Rolleman et al (2007)[8] | Low | Low | Low | Low | Low | Low | Unclear |
| Velikyan et al (2010)[9] | Low | Low | Low | Low | Low | Low | Low |
| Haug et al (2011)[10] | Low | Low | Low | Low | Low | Low | Low |
| Ayati et al (2017)[11] | Low | Low | Low | Low | Low | Low | Low |
| Aalbersberg et al (2018)[12] | Low | Low | Low | Low | Low | Low | Low |
| Cherk et al (2018)[13] | Low | Low | Low | Low | Low | Low | Unclear |
| Gälne et al (2019)[14] | Low | Low | Low | Low | Low | Low | Low |
| Jahn et al (2021)[15] | Low | Low | Low | Low | Low | Low | Low |
| Lodge et al (2021)[3] | Low | Low | Low | Low | Low | Low | Low |

decrease (between 10 and 60%) and 1 with a nonsignificant decrease. Data were scarcer for the kidneys' uptake, taking into consideration the proximity of the urinary tract, which may act as a confounding factor. A significant decrease in thyroid uptake was noted in 2 studies and in the pancreas in 1 study. A moderate increase in uptake was noted for the pituitary gland in Cherk and colleagues'[13] study. However, the difficulty of measuring this structure may have influenced the result (small size, attenuation correction artifacts).

## Effect of cSAs on Tumor Uptake

The time elapse between the 2 imaging studies should be taken into consideration. Indeed, cSAs have a long-term antitumor effect that could decrease tumor fixation due to a volumetric reduction and a partial volume effect.

In 5 studies, the 2 imaging procedures were performed within 1 month from each other.[3,5,6,9,12] Four of these 5 studies found an increase in the tumor–to–healthy organ ratio.[5,6,9,12] The last one, measuring tumor uptake without normalization, reported stability. These studies seem to indicate that cSAs have little or no effect on tumor uptake and that the increased ratios are driven by the decrease in the uptake of the surrounding organs.

This hypothesis seems to be confirmed by considering the 7 other studies, for which the delay between the 2 images was greater. Five of the 7 studies measured tumor uptake, without any ratio, and found no change[8,10,11,13] or a moderate decrease[15] under cSAs. The remaining 2 studies, using ratios, confirm an increased uptake.[7,14]

## Timing and Impact of Cold-to-Radiolabeled Ratio

The previously described effects seem to occur whether or not long-term treatment with cSAs has already been initiated. No negative impact on the tumor/healthy organ contrast was observed even when the injection of cSAs took place immediately before the radiotracer (up to 10 minutes before injection).

Bakker et al[16] reported complete saturation of SSTR in octreotide-pretreated rats with a cSA–to–$^{111}$In-pentetreotide ratio of 1000:1. In this experiment, the administration of cSAs prevented visualization of tumor lesions. We hypothesize that this ratio of 1000:1 is likely to be higher than that used in clinical routine and could explain the discrepancies with our results. However, the included studies only occasionally report the ratio between radiolabeled analogs and cSAs.

## Clinical Considerations

The benefit of treatment with cSAs is well documented in NETs.[2] Long administration of cSAs inhibits tumor growth and prolongs progression-free survival in patients with well-differentiated NETs[17] and helps to control the secretory syndrome.[2] Treatment with cSA is thus frequently encountered in patients referred for SSTR imaging for a NET.

Our results support the fact that there is no imperative to discontinue cSAs before SSTR imaging. On the contrary, treatment with cSAs before imaging, besides the known effects on symptoms and tumor growth, could improve the contrast and the performances of the examination, a phenomenon that is reminiscent of what has already been shown between $^{18}$F-FDOPA and cold carbiDOPA.[18] The increase in tumor-to-liver ratio results in better visualization of liver metastases. In clinical practice, this finding should be considered when SSTR imaging is performed for response monitoring.[18]

In perspective, the data collected could impact recommendations of procedure guidelines. More broadly, these results can also be applied to the field of theranostics: decreasing the uptake of healthy organs while preserving the tumor uptake could be very important for limiting the toxicity of $^{177}$Lu-labeled analogs.

**TABLE 2.** Studies' Design

| Study Data | | Tracer Administration | | Imaging Session 1 (Before Intervention) | | Intervention | | Imaging Session 2 (After Intervention) | |
|---|---|---|---|---|---|---|---|---|---|
| **Author (Year)** | **No. Patients** | **Tracer** | **Activity, MBq** | **Cold Octreotide Before Imaging** | **Protocol (Uptake Time Awaited)** | **Delay Imaging 1 Imaging 2** | **Octreotide Before Imaging 2** | **Last Administration of Cold Octreotide Before Imaging 2** | **Protocol (Uptake Time Awaited)** |
| Dörr et al (1993)[5] | 5 | [$^{111}$In] pentetreotide | 105–237 | None or withdrawal >24 h | Planar (30 min, 4 h, 24 h) | <28 d | Octreotide (600 μg/d, ongoing) | <1 d | Planar (30 min, 4 h, 24 h) |
| Soresi et al (1997)[6] | 12 | [$^{111}$In] pentetreotide | 110–130 | None | Planar (5 h) | 7 d | Octreotide (600 μg/d, 7 d) | <1 d | Planar (5 h) |
| Janson et al (1999)[7] | 8 | [$^{111}$In] pentetreotide | 114–238 | None | Planar (19–24 h) | 10–13 mo | Lanreotide (6000–12,000 μg/d) | 3 d | Planar (19–24 h) |
| Rolleman et al (2007)[8] | 10 | [$^{111}$In] pentetreotide | 220 | None | Planar (24 h) | 50–397 d | Octreotide (200–300 μg/d or LAR 20–30 mg/28 d) | 4–21 d (LAR) | Planar (24 h) |
| Velikyan et al (2010)[9] | 6 | [$^{68}$Ga] DOTATOC | 15–80 | None | Dynamic + whole body (50 min) | <1 d | Octreotide (50 μg, 250 or 500 μg, single dose) | 10 min | Dynamic + whole body (50 min) |
| Haug et al (2011)[10] | 9 | [$^{68}$Ga] DOTATATE | 200 | None | Whole body (60 min) | 13.8 wk | Octreotide LAR (20–50 mg/28 d) | NA | Whole body (60 min) |
| Ayati et al (2017)[11] | 30 | [$^{68}$Ga] DOTATATE | 110–185 | None | Whole body (60 min) | 9.6 mo | Octreotide LAR (30–60 mg/28 d) | 25.1 +/− 14.8 d | Whole body (60 min) |
| Aalbersberg et al (2018)[12] | 34 | [$^{68}$Ga] DOTATATE | 100 | Yes, imaging performed the day before the next administration | Whole body (45 min) | 2 d | Lanreotide LAR (60–120 mg/3–4 wk) | 1 d | Whole body (45 min) |
| Cherk et al (2018)[13] | 21 | [$^{68}$Ga] DOTATATE | 85–307 | None | Whole body (35–88 min) | 2–12 mo | Unspecified LAR (/28 d) | 21–28 d | Whole body (60 min) |
| Gålne et al (2019)[14] | 19 | [$^{68}$Ga] DOTATATE | 2.5/kg | None | Whole body (60 min) | 202 d | Unspecified LAR (/21 or /28 d) | Between 1 and 31 d | Whole body (60 min) |
| Jahn et al (2021)[15] | 4 | [$^{68}$Ga] DOTATOC | 167 | Yes, 7–27 d | Whole body (1 h) | 1–3.5 mo | Octreotide 400 μg (in addition to LAR treatment) | 15 min | Whole body (1 h, 4 h, 7 h) and dynamic studies in between |
| Lodge et al (2021)[3] | 7 | [$^{68}$Ga] DOTATOC | 185 | None | 8 Whole body (8–100 min) | 1–20 d | Octreotide (50 μg, single dose) | 10–15 min | 8 Whole body (8–100 min) |

**TABLE 3.** Studies' Results

| Author (Year) | Measure | Effect of cSAs on Tumor Uptake | | Effect of cSAs on Healthy Organ Uptake | | | |
|---|---|---|---|---|---|---|---|
| | | Histology | Tumor | Spleen | Liver | Kidneys | Others |
| Dörr et al (1993)[5] | Semiquantitative | NET | T/L: >20%* | Decrease (60%) | Decrease (28%) | Decrease (17%) | NA |
| Soresi et al (1997)[6] | Semiquantitative | SCLC | Increase in ratios<br>T/Lg: 1.98 vs 1.83<br>T/L: 0.78 vs 0.67 | NA | NA | NA | NA |
| Janson et al (1999)[7] | Semiquantitative | NET | T/B: +50% (−79% to 1085%) | Decrease (55%) | NA | NA | NA |
| Rolleman et al (2007)[8] | Semiquantitative | NET | T: NS (−15%) | Decrease (69%) | NS (decrease 17%) | NS (decrease 18%) | NA |
| Velikyan et al (2010)[9] | SUV | NET | T/L: increase (1%–223%) | Decrease (>40%*) | Decrease (>20%*) | Decrease (20%*) | NA |
| Haug et al (2011)[10] | SUV | NET | T: NS (21.7 vs 20.6) | NS (21.7 vs 23.3) | Decrease (7.1 vs 9.1) | NA | Adrenals: NS (7.8 vs 16.9) |
| Ayati et al (2017)[11] | SUV | NET | T: NS | Decrease (18.8 vs 24.5) | Decrease (7.6 vs 9.8) | NA | Adrenals: NS (14.6 vs 14.9)<br>Pituitary: NS (6.2 vs 6.3)<br>Thyroid: decrease (2.6 vs 3.9) |
| Aalbersberg et al (2018)[12] | SUV | NET | T/L: increase (2.59 vs 2.21) | Decrease (22.4 vs 25.8) | Decrease (9.1 vs 10.2) | NS (20.7 vs 19.8) | Adrenals: NS (20.6 vs 19.2)<br>Pituitary: NS (7.1 vs 6.6)<br>Parotid: NS (4.2 vs 4.0)<br>Thyroid: decrease (3.1 vs 4.1)<br>Bone marrow: NS (2.2 vs 2.4) |
| Cherk et al (2018)[13] | SUV | NET | T: NS | Decrease (23.1 vs 30.3) | Decrease (8 vs 10.3) | NA | Adrenals: NS<br>Pituitary: increase (11.9 vs 10.2)<br>Thyroid: decrease (3.5 vs 5.9) |
| Gålne et al (2019)[14] | SUV | NET | T/L: increase (5.6 vs 2.6) | NA | Decrease (6.0 vs 8.6) | NA | NA |
| Jahn et al (2021)[15] | SUV | NET | T: decrease (1 h: 0%–60%*) | Decrease (at 1 h: 60%–80%*) | Decrease (at 1 h: 40%–60%) | NA | Pancreas: decrease (40%–60%*) |
| Lodge et al (2021)[3] | SUV | NET | NS (12.8 vs 12.4) | Decrease (4.6 vs 8.8) | Decrease (2.7 vs 3.7) | NS (6.4 vs 6.2) | Red marrow: NS (1.1 vs 1.0)<br>Pituitary: NS (5.9 vs 7.4) |

Effects of cSAs on tumor or healthy organs' uptake are presented either as percentage value (%) or with changes in $SUV_{max}$ values.

*Estimated based on figures.

B, background; L, liver; Lg, lung; NA, not available; NS, nonsignificant; T, tumor.

## LIMITATIONS

The main limitation of this review is the number of analyzable patients in each study (from 4 to 34). However, SSTR imaging is now used primarily for NETs, which are inherently rare. The dosages and mode of administration of cSAs are heterogeneous in terms of quantity and rate of administration, as are the acquisition protocols for planar scintigraphy and PET/CT.

Considering the amount of data analyzed, a risk of collection bias is possible but limited by double reading at all stages of the inclusion process.

## CONCLUSIONS

The use of cSAs does not seem to alter the visualization of tumor lesions at SSTR imaging, being able to rather improve contrast by decreasing healthy organs' uptake, particularly in the liver.

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