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The impact of SSTR-directed PET/CT on the management of patients with neuroendocrine tumor: A systematic review and meta-analysis

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Running title: SSTR PET/CT management meta-analysis

ABSTRACT

Introduction: Somatostatin receptor (SSTR) imaging is widely used for guiding the management of neuroendocrine tumor (NET) patients. ^{68}Ga-DOTATATE approval by the US Food and Drug Administration has triggered widespread clinical interest in SSTR Positron Emission Tomography/Computed Tomography (PET/CT) throughout the US. Here we performed a systematic review and meta-analysis to evaluate the impact of SSTR PET/CT on the management of patients with NETs.

Methods: A comprehensive literature search was performed using The National Center for Biotechnology Information PubMed online database applying the following keywords: “management” AND “PET” AND “neuroendocrine”. Fourteen of 190 studies were deemed suitable based on the following inclusion criteria: original research, cohort study, number of patients ≥ 10, reported change in management after SSTR PET/CT. Change in management across studies was determined by a random effects model.

Results: A total of 1,561 patients were included. Overall, change in management occurred in 44% (range: 16-71%) of NET patients after SSTR PET/CT. In 4/14 studies SSTR PET/CT was performed after an ^{111}In-Octreotide scan. In this subgroup additional information by SSTR PET/CT led to a change in management in 39% (range: 16-71%) of patients. Seven/14 studies differentiated between inter- and intra-modality changes with the majority of changes being inter-modality (77%, intra-modality: 23%).

Conclusion: The management is changed in more than one third of patients undergoing SSTR PET/CT even when performed after an ^{111}In-Octreotide scan. Inter-modality changes were three times more likely than intra-modality changes underlining the clinical impact of SSTR PET/CT.

INTRODUCTION

NETs emerge from neuroendocrine cells most frequently from the bronchopulmonary or gastrointestinal system (*1*). Each year an estimated 8,000 individuals are newly diagnosed with NET in the United States and the annual incidence has increased five-fold since 1973 (*2*).

Accurate initial evaluation and detection of recurrence is paramount for all malignancies, including NETs. Traditionally, the diagnostic workup involved morphological imaging such as computed topography (CT), ultrasonography (US), or magnetic resonance imaging. These resulted in limited detection rates due to a variety of factors such as small size, variable location and low metabolic rates (*3*). It was later discovered that well differentiated NETs express high levels of SSTR, specifically subtype 2 (*4*). Therefore, in addition to conventional imaging, SSTR-targeted imaging could be applied to detect and functionally characterize NETs.

Somatostatin receptor scintigraphy using ^{111}Indium-DTPA-penteoctreotide (Octreoscan) was one of the first tracers developed to functionally image NETs. This probe binds with high affinity to SSTR, specifically subtypes 2 and 5 (*5*). Although considered a breakthrough at the time, Octreoscan suffered from limited image quality, limited spatial resolution, and prolonged imaging protocols (*6*). Over the past two decades, a number of chelator-conjugated somatostatin analogues were developed, among these DOTATATE, DOTANOC, and DOTATOC. These short amino acid-chelator conjugates demonstrated superior affinity for SSTR as compared to Octreoscan (*7,8*). DOTA-agents can be labeled with ^{68}Gallium, a generator eluted positron emitter that enables PET imaging and thus provides improved image quality and spatial resolution.

Several studies attest to the superior performance of ^{68}Ga labeled SSTR positron emission tomography (SSTR PET) compared to Octreoscan (*9-12*). This was recognized recently by the US Food and Drug Administration when it approved ^{68}Ga-DOTATATE (Netspot™, Advanced Accelerator Applications, Saint-Genis-Pouilly, France) as an imaging agent for the detection of NETs.

While the diagnostic performance of ^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, and ^{68}Ga-DOTANOC has been reported in detail (*11, 13-17*), the impact of SSTR PET/CT on patient management has not been reviewed systematically. The aim of this meta-analysis of published data was to determine the impact of SSTR PET/CT on the management of patients with NETs.

METHODS

Literature Search

A systematic literature search was performed using The National Center for Biotechnology Information PubMed online database. The following keywords were used for selection of studies: “neuroendocrine” AND “PET” AND “management”. A full list of publications obtained with this search strategy is given in the supplemental material. Fourteen of 190 publications were deemed suitable based on the following inclusion criteria: original research, cohort study, reported change in management after somatostatin receptor imaging, number of patients ≥ 10.

Data Extraction

The following information was extracted from the fourteen suitable studies: study type (prospective vs. retrospective), radioligand, sample size, change in management with type of management change (surgical vs. any) and intended vs. implemented change, data acquisition method, responding entity, state of disease (primary staging vs. restaging), prior conventional imaging (if applicable), and response rates.

Additionally, treatment changes were extracted from selected studies if the pre-scan and post-scan therapy recommendations were reported. Type of change was classified as inter- versus intra-modality. An inter-modality change was defined as change in the type of therapy (e.g. surgery to chemotherapy). An intra-modality change was defined as change in dose/approach/technique within the suggested treatment modality (e.g. change in surgical strategy).

Statistical Analysis

Descriptive statistics such as mean and standard deviation were used to summarize continuous variables, while count and percentage were used for categorical variables. The fixed-effects model

approach may not provide proper inference for the data set; so instead, we performed random-effects models for the overall impact on management for the 14 studies, as well as subgroup analysis with patients undergoing prior Octreoscan. The random-effects model estimates the magnitude of the heterogeneity, and assigns a greater variability to the estimate of overall change in management to account for this heterogeneity (*18*). Each study is weighted by the inverse of its variance (both for within-studies variance and between-studies variance). Consequently, individual study weights are more balanced, the impact of large trials decreases and the confidence interval for the combined effect increases in width as compared to the fixed-effects model. Model diagnostics were performed to assess the forest plots with 95% confidence interval. Tests for significance were two-tailed, with a statistically significant p-value threshold of 0.05. Statistical analyses were carried out using R version 3.1.3.

RESULTS

Study Characteristics

Upon systematic review, 14 studies were included. Nine (64%) were retrospective and 5 (36%) were prospective. ^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, and ^{68}Ga-DOTANOC, were used in 8 (57%), 3 (21%) and 3 (21%) studies, respectively. A total of 1,561 participants (737 males, 824 females; mean age 54 years, range: 15-86) were included. The largest dataset provided by Skoura et al. analyzed 728 patients retrospectively (*19*). The largest prospective study by Sadowski et al. (*20*) included 130 patients. The remaining 12 studies included 53% of all patients (on average 4% per study). Characteristics of the included studies are presented in Table 1.

Impact on Management

Impact on management for the 14 studies is illustrated in Figs. 1A-C. PET/CT findings resulted in management changes in 44% of the patients (CI: 36-51% range: 16-71%, Table 1, Fig. 1C). Studies on implemented management (Fig. 1A, Implemented Group) reported change in 44% (CI: 35-55%, range: 19-71%), studies on intended management (Fig. 1B, Intended Group) reported change in 41% (CI: 28-57%, range: 16-60%) of patients.

Four studies on 278 patients performed SSTR PET/CT in addition to a prior Octreoscan (Table 2) (*12, 20-22*). In this subgroup an average of 39% of patients (CI: 0.22-0.59%, range: 16-71%) experienced change in treatment strategy (Fig. 2). Fig. 3 demonstrates ^{68}Ga-DOTATATE PET/CT findings in a patient with prior Octreoscan (*23*).

Type of management change (inter- versus intra-modality) was documented in 7/14 (50%) studies. Overall, inter-modality changes (77%) occurred more than three times more frequently than intra-modality changes (23%) (Fig. 4, Table 3).

DISCUSSION

This manuscript provides a systematic analysis of the impact of SSTR PET/CT on the management in patients with NETs. Management changes were seen in 44% of all patients. No significant difference in the rate of management change was seen among reports of intended (41%) vs. implemented (44%) management change. Management was also changed in 39% of those patients who had undergone a prior Octreoscan. Finally, inter-modality management changes occurred three times more frequently than intra-modality changes.

The superior diagnostic performance of SSTR PET/CT as compared to Octreoscan has led to the recent US Food and Drug Administration approval of ^{68}Ga-DOTATATE as imaging agent for NET. Three clinical studies were highlighted in the prescribing information of ^{68}Ga-DOTATATE: Two trials demonstrated high accuracy using histopathology or clinical follow-up for lesion verification (*24,25*), one trial demonstrated safety and significant change in management in a head to head comparison with Octreoscan (*22*).

Impact on management is a prerequisite for acceptance of diagnostic tests by physicians and insurance companies. Centers for Medicare and Medicaid Services requested data on the impact of ^{18}F-FDG PET/CT on clinical management to recommend reimbursement. This was evaluated in the National Oncologic PET Registry that enrolled tens of thousands of patients and demonstrated intended management changes in around 40% of patients with a variety of cancers (*26*). Inter-modality changes were two times more likely than intra-modality changes (*26*). National Oncologic PET Registry findings led to wide coverage of ^{18}F-FDG PET/CT by the Centers for Medicare and Medicaid Services. The degree of impact of ^{18}F-FDG PET/CT is comparable to that of SSTR PET/CT regarding overall management changes (>40%) however the rate of inter- modality/major changes was higher for SSTR PET/CT (*26*).

The proportion of patients experiencing a change in management was similar in studies that reported intended (41%) vs. implemented (44%) changes. This suggests that trials with intended

endpoints do not suffer from low rates of implementation and underlines the validity of such endpoints. The additional value of SSTR PET/CT is robust and unaffected by prior SSTR scintigraphy. 39% of patients with prior Octreoscan experienced treatment changes highlighting the clinical impact of the more advanced PET/CT versus scintigraphy technology. Advantages also include the practicability of a two-hour PET/CT versus two day Octreoscan protocol, which was not analyzed by this meta-analysis.

Other limitations of this study should be noted: as with most meta-analyses, included articles were heterogeneous. Specifically, the definition of actual "change in management" varied from study to study. On the other hand, the majority of included studies focused on implemented changes (9/14, 64%) and findings for the proportion of patients experiencing change in management were similar across all subgroups (average 39 to 44%). Skoura et al. (*19*) provided about half (728/1561, 47%) of all the patients included in this study. Even though the change reported by Skoura et al. was well in range with results for the entire cohort, random effects model was used for analysis to avoid undue impact of this large trial.

CONCLUSION

Our systematic analysis demonstrates that PET/CT imaging using ^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, or ^{68}Ga-DOTANOC is vital for patient management. Change occurred in similar magnitude when compared to the National Oncologic PET Registry multicenter trial resulting in ^{18}F-FDG PET/CT reimbursement.

SSTR PET allows sensitive tumor detection. Based on its accuracy SSTR PET/CT is the standard of care in Europe, incorporated into clinical guidelines (*27*), and recently received approval in the US for the evaluation of NET. SSTR radioligands further serve as predictive biomarkers to confirm target receptor expression and identify patients suitable for ^{177}Lu-DOTATATE PRRT, currently under expanded

access. This systematic analysis demonstrates that accuracy translates into change in clinical management which underlines the importance of SSTR PET/CT implementation into the routine care of NET patients.

CONFLICTS OF INTEREST

K.H. and W.P.F are consultants of Ipsen and have a research agreement with Advanced Accelerator Applications (AAA).

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Table 1: Characteristics of Included Trials

Study	Timeline	Radioligand	Number of Patients	Change in management	Change in Management (Any or Surgical only)	Change in intended or implemented management	Response Rates	Data Acquisition (Review or Questionnaire)	Responding Entity	State of Disease (Primary or, Any)	Prior Conventional Imaging**
Frilling et al. 2010[28]	Retrospective	^{68}Ga-DOTATOC	52	31 (60%)	Any	Implemented	100%	Review	Independent expert commission	Any	Yes
Ambrosini et al. 2010[29]	Retrospective	^{68}Ga-DOTANOC	90	32 (36%)	Any	Implemented	N/A	Questionnaire	Referring physician	Any	Yes
Ruf et al. 2010[30]	Retrospective	^{68}Ga-DOTATOC	64	24 (38%)	Any	Implemented	97%	Review	Independent expert commission	Any	Yes
Srirajaskanthan et al. 2010[21]	Retrospective	^{68}Ga-DOTATATE	51	36 (71%)	Any	Implemented	16%	Review	Independent expert commission	Any	Yes
Naswa et al. 2011[23]	Prospective	^{68}Ga-DOTANOC	109	21 (19%)	Any	Implemented	100%	Review	Referring physician	Any	Yes
Krausz et al. 2011[12]	Prospective	^{68}Ga-DOTANOC	19	3 (16%)	Any	Intended	100%	Review	Referring physician	Any	Yes
Froeling et al. 2012[32]	Retrospective	^{68}Ga-DOTATOC	21	10 (48%)	Any	Implemented	N/A	Review	Referring physician	Any	No
Hofman et al. 2012[33]	Retrospective	^{68}Ga-DOTATATE	59	34 (58%)	Any	Implemented	N/A	Review	Independent expert commission	Any	Yes
Has Simsek et al. 2014[34]	Prospective	^{68}Ga-DOTATATE	27	16 (59%)	Any	Intended	100%	Review	Independent expert commission	Any	Yes
Herrmann et al. 2015[31]	Prospective	^{68}Ga-DOTATATE	88	53 (60%)	Any	Intended	88%	Questionnaire	Referring physician	Any	Yes
Ilhan et al. 2015[35]	Retrospective	^{68}Ga-DOTATATE	44	9 (20%)	Surgical Only	Implemented	N/A	Review	Independent expert commission	Primary	No
Sadowski et al. 2015[20]	Prospective	^{68}Ga-DOTATATE	130	43 (33%)	Any	Intended	100%	Review	Referring physician	Any	Yes
Skoura et al. 2016[19]*	Retrospective	^{68}Ga-DOTATATE	1,258*	515* (41%)	Any	Implemented	N/A	Review	Independent expert commission	Any	Unknown
Deppen et al. 2016[22]	Retrospective	^{68}Ga-DOTATATE	78	28 (36%)	Any	Intended	80%	Review	Independent expert commission	Any	Yes

*This study recorded the total number of scans and was analyzed on a “per scan” basis; the number of patients in their study was 728

**Conventional imaging includes bone scan, ultrasound, magnetic resonance imaging, CT, Octreoscan, and ^{18}F-FDG PET/CT

Table 2: Change in management in patients with prior Octreoscan

Study	Radioligand	Number of Patients	Change in management
Srirajaskanthan et al. 2010[21]	^{68}Ga-DOTATATE	51	36 (71%)
Krausz et al. 2011[12]	^{68}Ga-DOTANOC	19	3 (16%)
Sadowski et al. 2015[20]	^{68}Ga-DOTATATE	130	43 (33%)
Deppen et al. 2016[22]	^{68}Ga-DOTATATE	78	28 (36%)

Table 3: Inter- versus intra-modality management change

Study	Radioligand	Number of Patients	Overall Change in management	Inter-modality change*	Intra-modality change*
Frilling et al. 2010[28]	^{68}Ga-DOTATOC	52	31 (60%)	17 (55%)	14 (45%)
Froeling et al. 2012[32]	^{68}Ga-DOTATOC	21	10 (48%)	4 (40%)	6 (60%)
Hofman et al. 2012[33]	^{68}Ga-DOTATATE	59	34 (58%)	28 (82%)	6 (18%)
Has Simsek et al. 2014[34]	^{68}Ga-DOTATATE	27	16 (59%)	15 (100%)**	0 (0%)
Herrmann et al. 2015[31]	^{68}Ga-DOTATATE	88	53 (60%)	52 (98%)	1 (2%)
Ilhan et al. 2015[35]	^{68}Ga-DOTATATE	44	9 (20%)	5 (55%)	4 (45%)
Deppen et al. 2016[22]	^{68}Ga-DOTATATE	78	28 (36%)	19 (68%)	9 (32%)

* Percentages are with respect to number of patients who had a change in management

** Conflicting data: 15 patients are listed with a change in management, even though the article text reports 16

Figure Legends

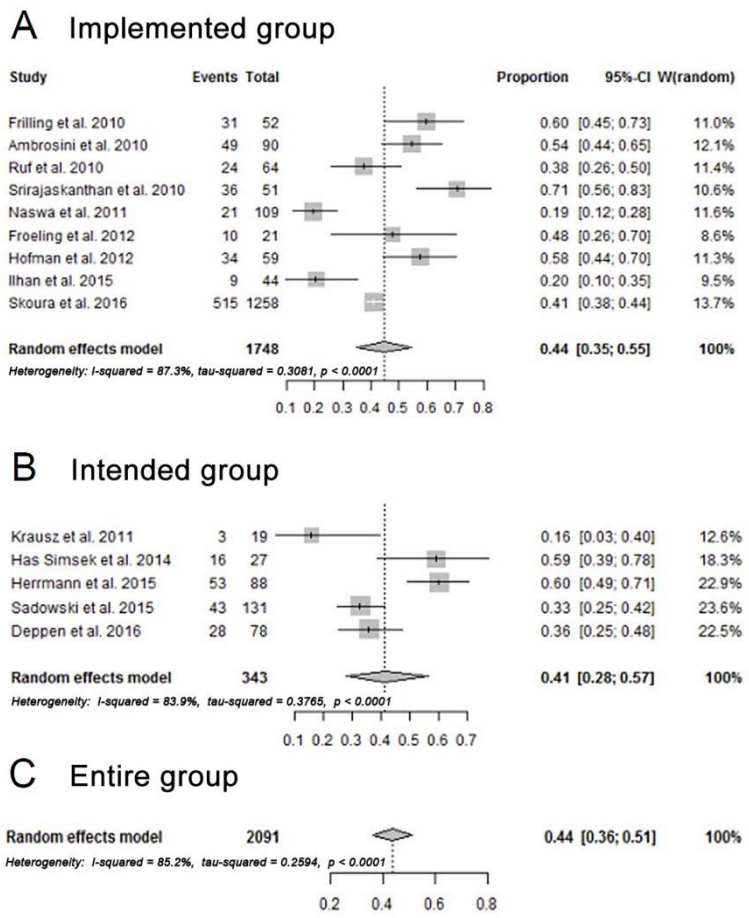

Figure 1: Analysis of the change in management separated by implemented (A) and intended (B) changes and for all included studies (C).

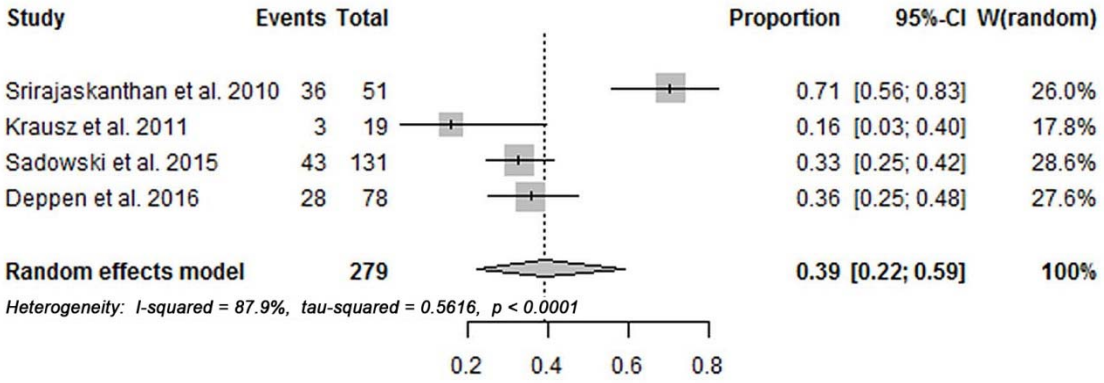

Figure 2: Subgroup analysis of patients who underwent Octreoscan prior to the SSTR PET/CT.

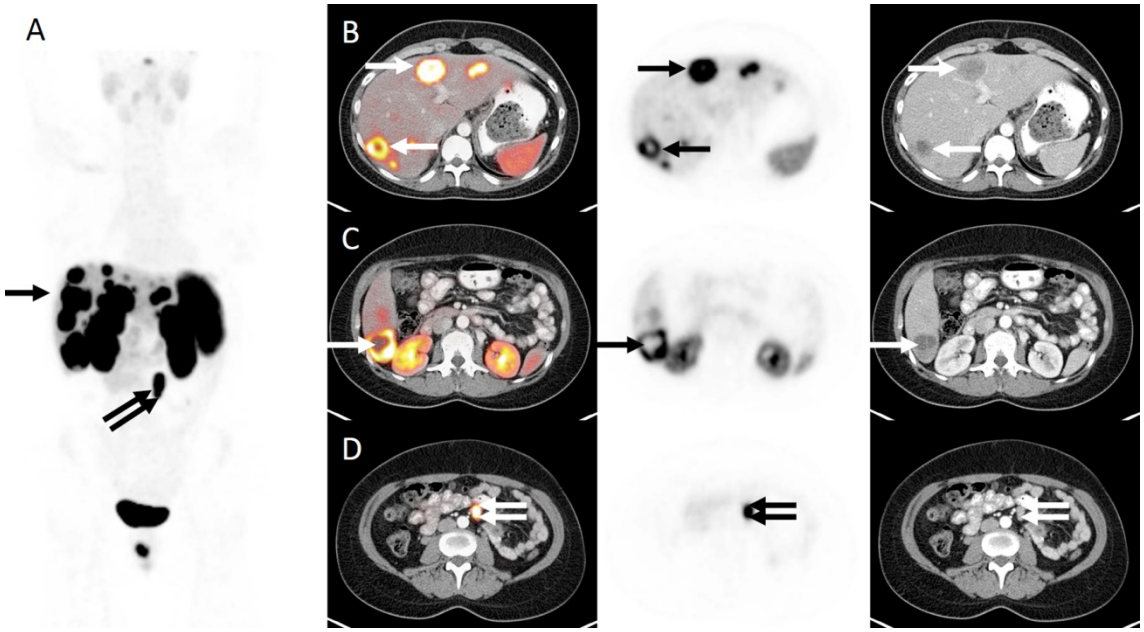

Figure 3: 38-year-old female patient with metastatic NET of unknown primary. Octreoscan revealed SSTR-positive liver metastases. No extrahepatic disease was noted. The intended management was somatostatin-analogue therapy. Maximum-intensity projection (A) and axial images of ^{68}Ga-DOTATATE PET/CT performed two months after Octreoscan are shown. PET/CT revealed numerous liver lesions (rows B, C) with intense tracer uptake (arrow). In addition, a left mesenteric mass was discovered (row D, double arrow), which was later confirmed to be a small bowel primary. Surgery for the small bowel primary and initiation of somatostatin-analogue therapy was implemented two months after ^{68}Ga-DOTATATE PET/CT scan.

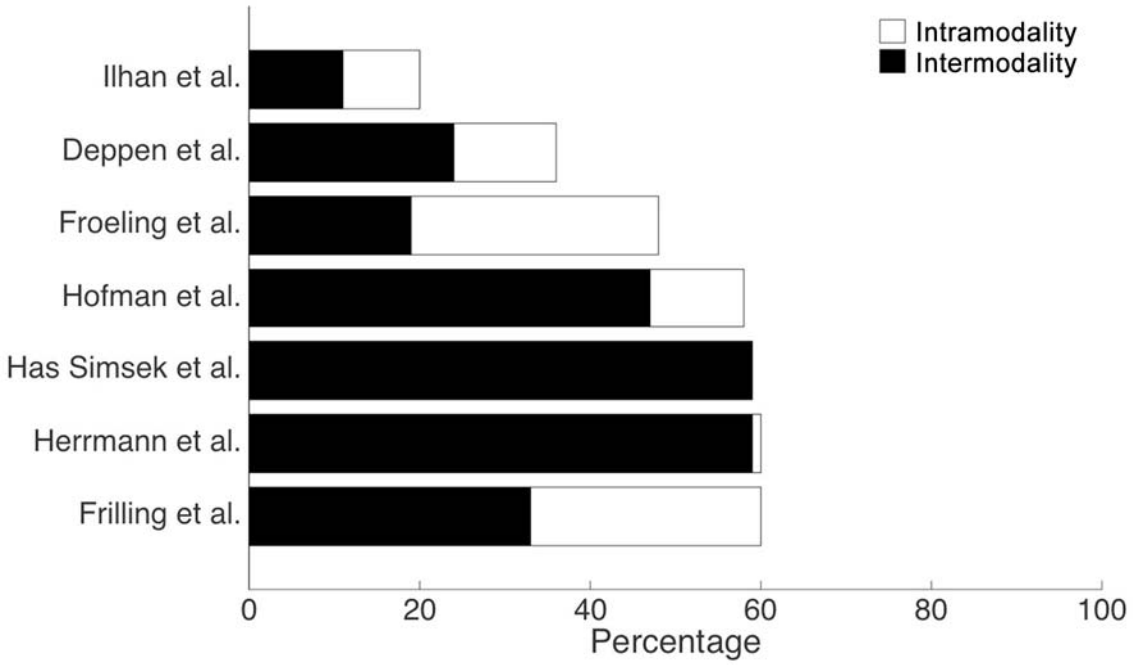

Figure 4: Type of change was differentiated in 7 of the 14 (50%) studies. Bars represent proportion of patients with any change in management, separated by subgroups with intermodality (black) vs. intramodality (white) change.