Evaluating Xerostomia as a side effect of [^{255}Ac]Ac-PSMA therapy in prostate cancer: a systematic review and meta-analysis

Akram Al-Ibraheem[1,2,*], Serin Moghrabi[1], Mike Machaba Sathekge[3,4,5], Ahmed Saad Abdlkadir[1]

[1] Department of Nuclear Medicine, King Hussein Cancer Center (KHCC), Queen Rania Street Al Jubeiha, Amman 11941, Jordan

[2] School of Medicine, The University of Jordan, Amman 11942, Jordan [3] Department of Nuclear Medicine, University of Pretoria & Steve Biko Academic Hospital, Pretoria 0001, South Africa

[4] Nuclear Medicine Research Infrastructure (NuMeRI), Steve Biko Academic Hospital, Pretoria 0002, South Africa

[5]Department of Nuclear Medicine, Steve Biko Academic Hospital, Pretoria 0001, South Africa

*Correspondence to Akram Al-Ibraheem. Email: aibraheem@khcc.jo; akramalibrahim@gmail.com

Serin Moghrabi. Email: sm.16471@khcc.jo

Mike Machaba Sathekge. Email: mike.sathekge@up.ac.za

Ahmed Saad Abdlkadir. Email: ahmedshukri92@hotmail.com

Abstract

Purpose: This systematic review and meta-analysis evaluates xerostomia occurrence in prostate cancer (PC) patients undergoing [^{225}Ac]Ac-prostate-specific membrane antigen ([^{225}Ac]Ac-PSMA) therapy.

Methods: Following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines, comprehensive electronic searches were conducted across PubMed, Scopus, and Web of Science. The study included articles addressing xerostomia as a side effect of [^{225}Ac]Ac-PSMA therapy in clinical settings, encompassing both tandem and monotherapy strategies. Methodological quality was assessed using the National Institutes of Health (NIH) Assessment Tool. Stata software was employed to perform pooled xerostomia rates, heterogeneity analysis, meta-regression, and publication bias analysis.

Results: Twenty studies met inclusion criteria, comprising 2949 [^{225}Ac]Ac-PSMA cycles administered to 1207 PC patients. For [^{225}Ac]Ac-PSMA monotherapy, the pooled rate of any-grade xerostomia was 84% (95%CI: 69–94%). Grade 1–2 xerostomia had a pooled rate 83% (95%CI: 71–93%), while therapy discontinuation due to xerostomia was 5% (95%CI: 0–13%). Grade 3 xerostomia was evident in 13% (95%CI: 7–20%). [^{225}Ac]Ac/[^{177}Lu]Lu-PSMA tandem therapy resulted in lower pooled rate of 68% for grade 1–2 toxicity (95%CI: 17–100%). Indirect comparison revealed a two-fold decrease in xerostomia risk with tandem protocol compared to monotherapy. Significant heterogeneity was observed, primarily influenced by baseline median prostate-specific antigen values ($p = 0.04$). Publication bias was present in

most xerostomia subgroups, with trim-and-fill analysis adjusting for effect size in specific categories.

Conclusion: Xerostomia is most pronounced in patients undergoing [^{225}Ac]Ac-PSMA monotherapy. Tandem approach with [^{177}Lu]Lu-PSMA could reduce xerostomia rates and improve compliance. Further large-scale, prospective studies are necessary for generalization and result consolidation.

Keywords: [^{225}Ac]Ac-PSMA; Xerostomia; Dry mouth; Tandem; Targeted alpha therapy; Meta-analysis

Introduction

Prostate cancer (PC) is currently the second most prevalent cancer and the fifth leading cause of cancer-related mortality among men worldwide according to the latest report of global cancer statistics in 2022 [1]. PC can progress to a more severe stage known as metastatic castration-resistant form (mCRPC), which is resistant to conventional hormonal therapy, manifested by rapid disease progress, and accelerated metastases [2]. Treatment options for mCRPC have significantly evolved with advancements in radiopharmaceuticals, where radionuclides are labeled to ligands targeting type II membrane glycoprotein that is overexpressed on prostate cancer cells, called prostate-specific membrane antigen (PSMA) [3].

The beta-emitting [^{177}Lu]Lu-PSMA-617 has shown considerable effectiveness, as studies indicate a prostate-specific antigen (PSA) response rate of approximately 60–70% and a median progression-free survival of around 8 months in patients with advanced prostate cancer [4]. However, clinical trials have revealed that up to 37% of patients are refractory to [^{177}Lu]Lu-PSMA-617 [5].

[^{225}Ac]Ac-PSMA therapy is an emerging alpha-emitting treatment for advanced prostate cancer, particularly effective for patients who are refractory to [^{177}Lu]Lu-PSMA therapy [6]. This novel therapy agent leverages the high linear energy transfer (LET) properties of [^{225}Ac]Ac, which enables the delivery of potent alpha particles directly to PSMA-expressing cells. The high LET characteristic of [^{225}Ac]Ac results in more effective double-strand DNA breaks in cancer cells [7].

Studies have shown that [^{225}Ac]Ac-PSMA therapy has demonstrated promising efficacy in patients who have progressed on [^{177}Lu]Lu-PSMA, with 88.5% experiencing any decline in PSA levels and 65.4% achieving a significant PSA decline of 50% or more with median overall survival (OS) of around 7.7 months [8]. However, the manifestation of xerostomia poses a notable challenge in the management of treatment-related adverse events [9]. This challenge arises from the fact that PSMA is expressed not only in prostate cancer and prostate tissue but also in the salivary glands. In fact, PSMA exhibits extended intracellular retention within the salivary glands as a result of the internalization of the radiopharmaceutical [10]. Xerostomia, characterized by a subjective sensation of oral dryness due to decreased salivary flow, can pose significant health concerns and lead to numerous oral health disorders [11]. Patients often experience discomfort or pain during mastication, necessitating frequent water intake [12]. Reduced salivary output can also affect taste perception, damage taste receptors, and impair taste discrimination [13]. This impairment, occurring early during therapy, is most pronounced

with bitter and salty flavors [13]. The risk of dental caries increases due to factors such as cariogenic flora, changes in salivary pH, immunoglobulin composition, and decreased mineralizing components [14]. Diminished salivary flow may also elevate the risk of mandibular osteonecrosis and esophageal injury [15]. Oral mucosal dryness can predispose individuals to mucosal fissures and ulcerations [16]. These secondary effects contribute to xerostomia syndrome, potentially leading to decreased nutritional intake and weight loss, a significant health concern for some patients [17]. Current classification by version 5.0 of the Common Terminology Criteria for Adverse Events (CTCAE) [18], identifies three grades of xerostomia (Table 1). The onset of xerostomia can significantly diminish patient comfort and satisfaction, potentially leading to treatment discontinuation or dose reduction, thereby compromising therapeutic outcomes [19].

Table 1. Grades of xerostomia. Adapted from common terminology criteria for adverse events (CTCAE) version 5.0. TPN, total parenteral nutrition

Dry Mouth	Symptoms	Salivary flow	Diet restriction	Food Intake
Grade 1	Asymptom-atic-mild symptoms	>0.2 ml/min	None	Orally
Grade 2	Moderate symptoms	0.1–0.2 ml/min	Partial: Limited to soft and moist food	Orally
Grade 3	Severe symptoms	<0.1 ml/min	Total: Inability to adequately aliment orally	Tube feed-ing or TPN

This systematic review and meta-analysis investigates the pooled rates of xerostomia in prostate cancer patients undergoing [^{225}Ac]Ac-PSMA therapy. Both qualitative and quantitative metrics have been employed to examine the outcome of interest.

Methods

Data synthesis

We conducted a systematic review and meta-analysis of relevant studies adhering to the guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement [20]. The study protocol was officially registered in PROSPERO, obtaining the registration number CRD42024618811. Three authors (AA, SM, and ASA) independently performed electronic searches of PubMed, Scopus, and Web of Science databases to identify published manuscripts exploring xerostomia as a side effect of [^{225}Ac]Ac-PSMA therapy in prostate cancer. Our search strategy incorporated various MeSH and Emtree key terms related to xerostomia in [^{225}Ac]Ac-PSMA therapy [21], with the final update conducted on May 1, 2024. We included only articles specifically addressing xerostomia as a side effect of [^{225}Ac]Ac-PSMA therapy in prostate cancer patients in clinical settings, encompassing both tandem and monotherapy strategies. During initial screening, we excluded duplicate studies, book chapters, conference papers, abstracts, preclinical studies, and irrelevant articles. Full texts of potentially relevant studies were retrieved for detailed examination. A cross-reference search ensured comprehensive inclusion of relevant studies.

Retrieved data were imported into Microsoft Excel Professional Plus 2024 software (Redmond, Washington, United States) for organization, sorting, screening, and filtering.

Data collection

A comprehensive retrieval and analysis of studies meeting the inclusion criteria for the systematic review and meta-analysis was conducted. A dedicated Microsoft Excel spreadsheet was created to facilitate a systematic, in-depth examination of the selected articles. Pertinent data were meticulously extracted from each study, including the primary author's name, publication year, country of correspondence, article type, research design, patient cohort size, median age, prior therapy lines, [^{225}Ac]Ac-PSMA treatment strategy and dose, number of [^{225}Ac]Ac-PSMA cycles, metastatic pattern, Eastern Cooperative Oncology Group (ECOG) performance status, xerostomia grades as per CTCAE version 5.0 [18], and median PSA values.

Assessment of methodological quality

The quality of the included studies was thoroughly assessed using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [22]. This comprehensive evaluation, based on 14 criteria, examined each study's methodological strengths and limitations, thereby enhancing the reliability and validity of our review findings. We adopted the NIH quality scoring system, which categorizes studies into three distinct quality levels based on numerical scores. Studies classified as "Good" achieved scores between 9 and 14 points, those rated as "Fair" received scores between 5 and 8 points, and studies in the "Poor" category scored between 0 and 4 points [22].

Statistical analysis

This systematic review and meta-analysis examines the pooled proportions of each xerostomia grade induced by [^{225}Ac]Ac-PSMA as monotherapy or as part of a tandem strategy, employing a random-effects model. Pooled odds ratios and 95% confidence intervals (CIs) were calculated to assess the risk of xerostomia associated with monotherapy or tandem therapy. Utilizing Bucher's method, an indirect odds ratio was derived to outline the odds difference between the two treatment strategies [23]. Heterogeneity assessment was facilitated using the inconsistency (I^2) index, with values less than 50% indicating low heterogeneity and values greater than 50% indicating substantial heterogeneity [24]. A meta-regression analysis was conducted to assess potential sources of heterogeneity. The Doi plot and Luis Furuya-Kanamori (LFK) index were employed to determine the presence of publication bias related to each xerostomia grade [25]. On the Doi plot, a symmetrical graph with LFK index values within ± 1 implies no asymmetry, values between ± 1 and ± 2 suggest minor asymmetry, and values exceeding ± 2 indicate major asymmetry [25]. Any asymmetry was addressed using Duval and Tweedie's trim and fill method to adjust study sample size and effect size when applicable [26]. A statistical significance threshold of $p < 0.05$ was established. Data analysis was conducted using Stata software version 17.0.

Results

Search results

This systematic review initially identified a total of 179 articles from three different databases (Scopus: 96 articles; Web of Science: 44; PubMed: 39 articles). After removing 50 duplicates,

129 titles, and abstracts were screened, with the majority of the articles not aligning with the study's objectives. Ultimately, only 20 articles met the criteria for inclusion in the systematic review (Fig. 1a). All studies employed [^{225}Ac]Ac-PSMA therapy under compassionate use provisions, with 19 out of 20 of the included studies exhibiting a retrospective design [7, 27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44].

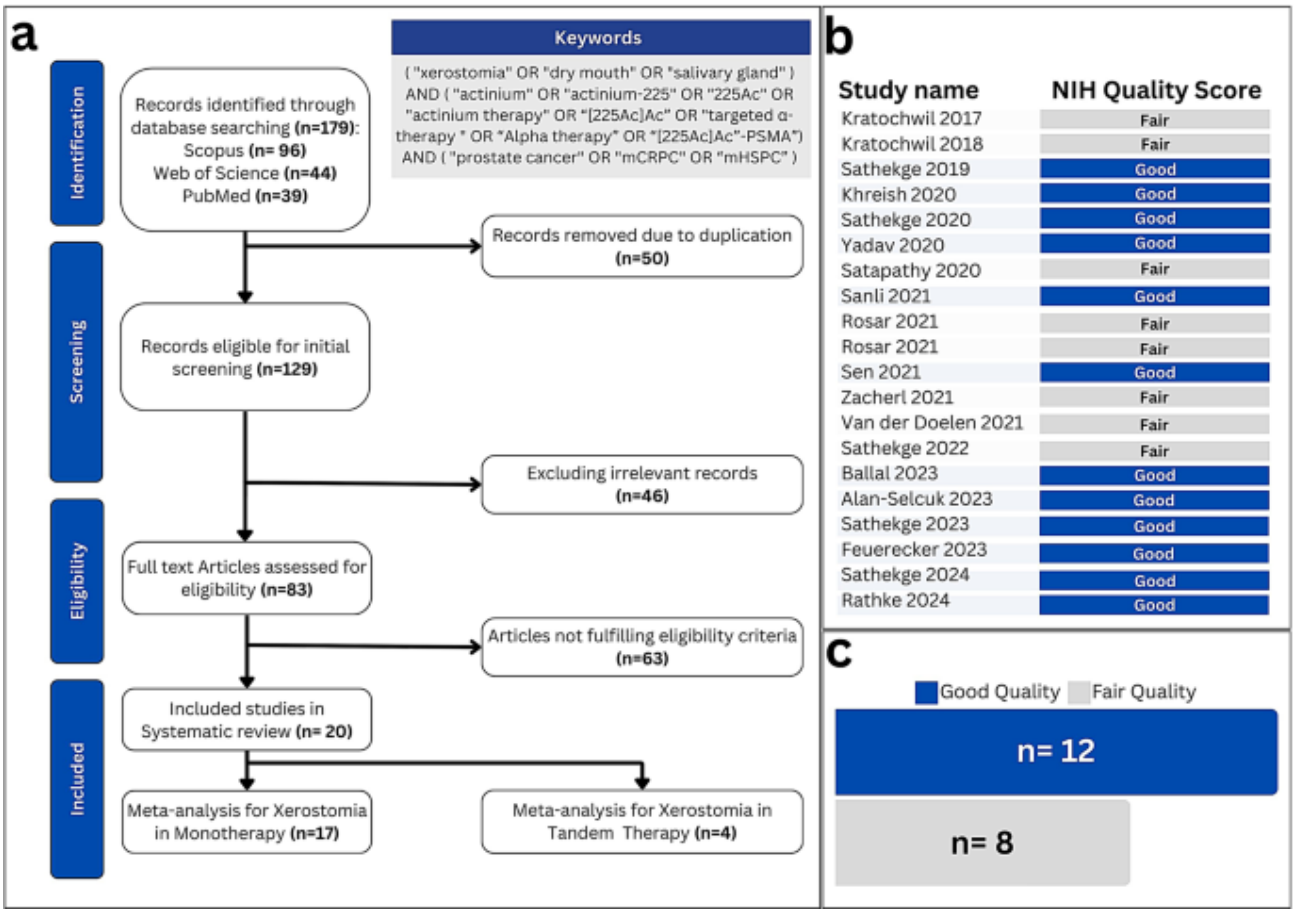

Fig. 1. (**a**) Graphical presentation of Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) flowchart. (**b, c**) Results of methodological quality as per National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Methodological quality

Utilizing the National Institutes of Health (NIH) Quality Assessment Tool, we evaluated the methodological quality of the 20 articles included in this systematic review. The assessment revealed that 12 articles met the criteria for "Good" quality [27,28,29,30, 33, 36, 37, 39,40,41,42, 45], while the remaining eight articles [7, 31, 32, 34, 35, 38, 43, 44], were categorized as "Fair" (Fig. 1b, c). Detailed information regarding the methodological quality evaluation is presented in Supplementary Table 1.

Systematic review

This systematic review analyzed 20 studies published between 2017 and 2024, encompassing 2,949 [^{225}Ac]Ac-PSMA cycles administered to 1,207 PC patients [7, 27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45]. The median age at presentation ranged from 62 to 77 years. Nineteen studies employed a retrospective design [7, 27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44], reflected unicentric experience [7, 27,28,29,30,31,32,33,34,35,36,37,38,39,40, 42,43,44,45], enrolled mCRPC patients [7, 27,28,29,30,31,32,33,34,35,36,37,38,39, 41,42,43,44,45], and utilized [^{225}Ac]Ac-PSMA-617 [7, 27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43, 45]. A single study adopted a prospective design [45], reflected multicentric experience [41], enrolled metastatic hormone-sensitive PC patients [40], and utilized [^{225}Ac]Ac-PSMA-I&T [44]. Three studies included Taxane naïve patients [37, 38, 40]. Five studies included [^{177}Lu]Lu-PSMA-617 naïve patients [32,33,34, 38, 40]. Fourteen studies included heavily pretreated patients [7, 27,28,29,30,31, 34, 36, 39, 41,42,43,44,45]. Eleven studies were conducted in Europe [27, 29,30,31,32,33,34,35,36, 43, 44], followed by five studies from South Africa [37,38,39,40,41], and four from India [7, 28, 42, 45]. [^{225}Ac]Ac-PSMA monotherapy was employed in 17 studies [7, 27,28,29, 31,32,33, 36,37,38,39,40,41,42,43,44,45], while [^{225}Ac]Ac/[^{177}Lu]Lu-PSMA tandem therapy was utilized in 4 studies [30, 33,34,35]. Notably, one study incorporated two matched subcohorts: one exposed to [^{225}Ac]Ac/[^{177}Lu]Lu-PSMA tandem therapy and the other to [^{225}Ac]Ac-PSMA monotherapy [33]. [^{225}Ac]Ac-PSMA-induced xerostomia events were reported in all studies [7, 27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45]. Table 2 presents the main features of systematic review-eligible papers.

Table 2. Key features for systematic review-eligible articles. CC, country of correspondence; DE, Germany; heavy pretreatment; denotes exhaustion of multiple therapy lines (including hormonal, chemotherapy, and radiotherapy) with or without prior [^{177}Lu]Lu-PSMA; IN, India; M, [^{225}Ac]Ac-PSMA monotherapy; NL, Netherlands; OP, original prospective; OR, original retrospective; PSMA, Prostate-specific membrane antigen; T, [^{225}Ac]Ac/[^{177}Lu]Lu-PSMA tandem therapy; TR, Turkey; ZA, South Africa

Study	CC	Sample Size	Median Age	Study Design	Protocol	PSMA Conjugate	Prior [177Lu]Lu-PSMA	Prechemotherapy	Heavy Pretreatment
Kratochwil 2017 [31]	DE	14	68	OR	M	617	21.4%	92.9%	Yes
Kratochwil 2018 [32]	DE	40	70	OR	M	617	0	75.0%	No
Sathekge 2019 [37]	ZA	17	65	OR	M	617	17.6%	0	No
Sathekge 2020 [39]	ZA	73	69	OR	M	617	19.2%	50.7%	Yes
Yadav 2020 [45]	IN	28	70	OP	M	617	53.6%	71.4%	Yes
Khreish 2020 [30]	DE	20	72	OR	T	617	100	65.0%	Yes
Satapathy 2020 [7]	IN	11	68	OR	M	617	45.5%	90.9%	Yes
Sanli 2021 [36]	TR	12	70	OR	M	617	58.3%	75.0%	Yes
Rosar 2021 [34]	DE	17	69	OR	T	617	100	76.5%	Yes
Rosar 2021 [35]	DE	15	77	OR	T	617	0	66.7%	No
Sen 2021 [42]	IN	38	68	OR	M	617	23.7%	100	Yes
Zacherl 2021 [44]	DE	14	75	OR	M	I&T	78.6%	78.6%	Yes
Van der Doelen 2021 [43]	NL	13	71	OR	M	617	15.4%	100	Yes
Sathekge 2022 [38]	ZA	53	63	OR	M	617	0	0	No
Ballal 2023 [28]	IN	56	67	OR	M	617	48.2%	100	Yes
Alan-Selcuk 2023 [27]	TR	23	70	OR	M	617	100	95.7%	Yes
Sathekge 2023 [40]	ZA	21	67	OR	M	617	0	0	No
Feuerecker 2023 [29]	DE	21	69	OR	M	617	100	100	Yes
Sathekge 2024 [41]	ZA	488	68	OR	M	617	31.6%	66.4%	Yes
Rathke 2024 [33]	DE	104	62	OR	M	617	0	70.2%	No
		129	62		T	617	0	69.8%	No

Meta-Analysis: [225Ac]Ac-PSMA monotherapy

A total of 17 studies reported xerostomia of any grade affecting 758 patients during the administration of 2,596 cycles of [^{225}Ac]Ac-PSMA monotherapy [7, 27,28,29, 31,32,33, 36,37,38,39,40,41,42,43,44,45]. The pooled proportion rate was 84% (95% CI: 69–94%). Grade 3 xerostomia was reported in five studies [7, 29, 31, 32, 42], affecting 16 patients during the administration of 214 [^{225}Ac]Ac-PSMA monotherapy cycles, with a pooled rate of 13% (95% CI: 7–20%). Discontinuation of [^{225}Ac]Ac-PSMA therapy was observed in three studies [31, 32, 41], impacting a total of 16 patients, with a pooled rate of 5% (95% CI: 0–13%). Sixteen studies reported grade 1–2 xerostomia affecting 741 patients during the administration of 2,476 cycles of [^{225}Ac]Ac-PSMA monotherapy [7, 27,28,29, 31,32,33, 36,37,38, 40,41,42,43,44,45], with a pooled proportion rate of 83% (95% CI: 71–93%). Significant heterogeneity was observed during pooled analysis of grade 1–2 xerostomia and xerostomia of any grade ($I^2 > 93\%$, $p = 0.00001$ for each). Figure 2 presents the forest plots for the subgroup meta-analyses.

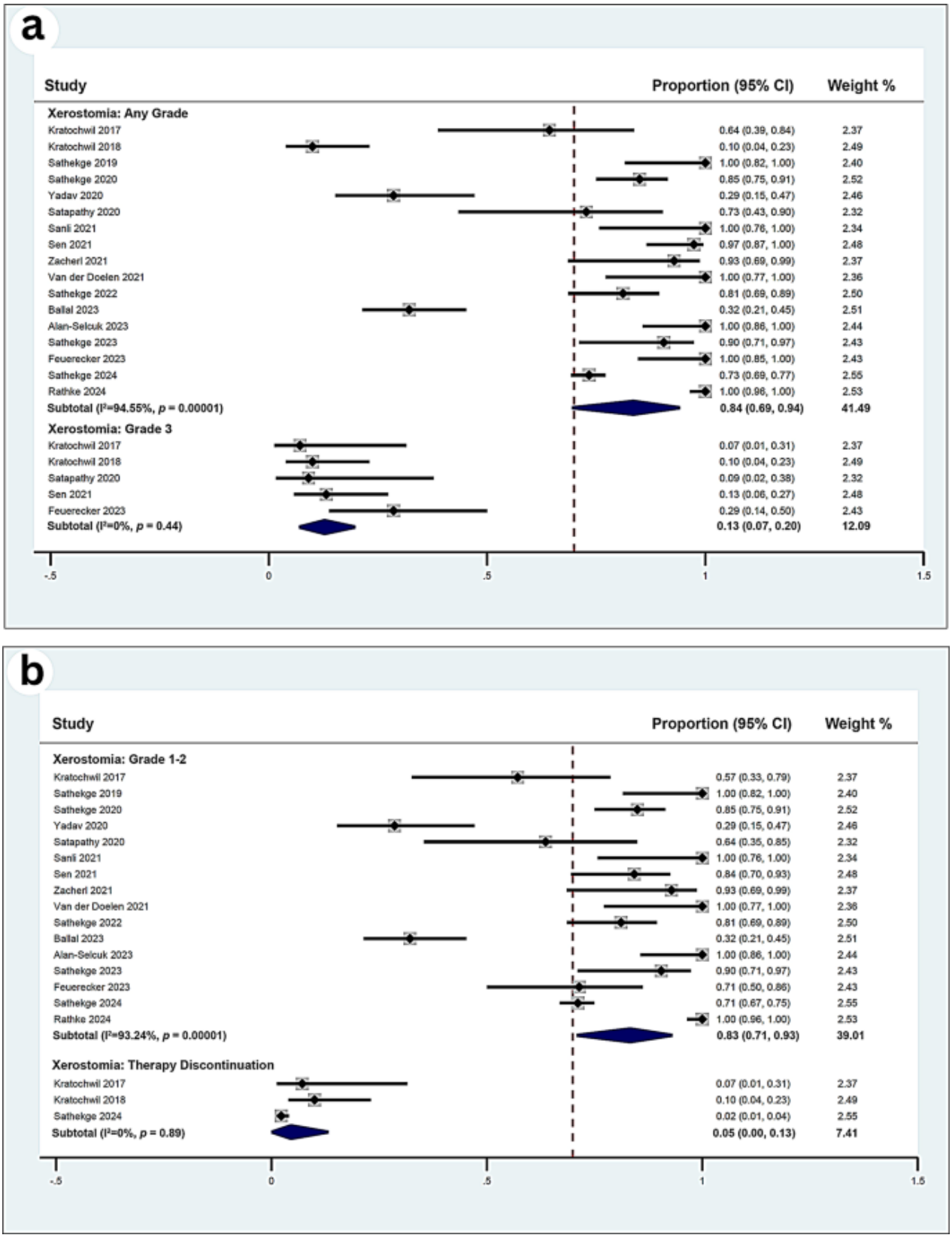

Fig. 2. (**a, b**) Forest plots for xerostomia pooled proportion subgroup meta-analyses according to toxicity grades of [^{225}Ac]Ac-PSMA Monotherapy

Meta-Analysis: [225Ac]Ac/[177Lu]Lu-PSMA tandem therapy

Four studies reported xerostomia of any grade affecting 155 patients during the administration of 353 cycles of [^{225}Ac]Ac/[^{177}Lu]Lu-PSMA tandem therapy. The pooled proportion rate was 68% (95% CI: 17–100%). All affected patients developed low-grade (1–2) xerostomia. Notably, no therapy discontinuation or grade 3 xerostomia was reported in patients undergoing the [^{225}Ac]Ac/[^{177}Lu]Lu-PSMA tandem protocol. Substantial heterogeneity was observed among the studies ($I^2 = 96.7\%$; $p = 0.0001$). Figure 3 presents the forest plots for the subgroup meta-analyses.

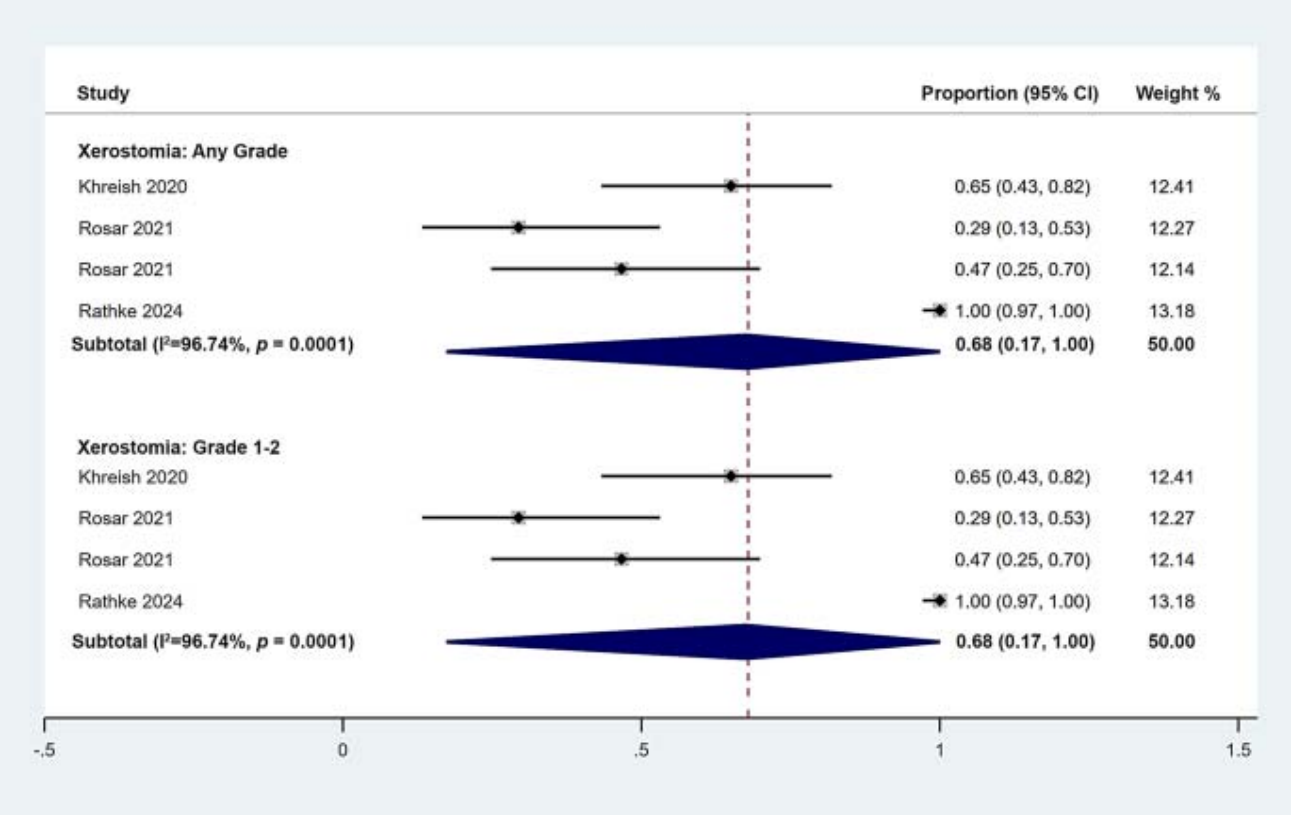

Fig. 3. Forest plots for xerostomia pooled proportion subgroup meta-analyses according to toxicity grades of [^{225}Ac]Ac/[^{177}Lu]Lu-PSMA Tandem Protocol

Monotherapy vs. tandem approach to PSMA-related Xerostomia

Utilizing Bucher's method, we conducted indirect comparisons of pooled odds ratios for xerostomia events across [^{225}Ac]Ac-PSMA treatment protocols. [^{225}Ac]Ac-PSMA monotherapy administered at a median dose of ≥ 100 KBq/kg demonstrated a pooled odds ratio of 2.4 (95% CI: 2.1–2.8). This value was significantly higher than that observed for [^{225}Ac]Ac/[^{177}Lu]Lu-PSMA tandem therapy administered at a [^{225}Ac]Ac-PSMA median dose of 60 KBq/kg (pooled odds ratio: 1.1; 95% CI: 0.6–1.9; $p = 0.0001$). The derived indirect odds ratio of 2.2 indicates that [^{225}Ac]PSMA monotherapy is associated with approximately twice the risk of developing xerostomia of any grade compared to tandem therapy (Table 3).

Table 3. Results of indirect odds ratio

Classification	Odds Ratio	95% CI	*p*-value
[^{225}Ac]Ac-PSMA Monotherapy	2.4	2.1–2.8	0.0001
[^{225}Ac]Ac/[^{177}Lu]Lu-PSMA Tandem Therapy	1.1	0.6–1.9	
Indirect Comparison	2.2	1.2–3.95	

Meta-regression analysis

Meta-regression analysis was employed to assess influential factors affecting heterogeneity. Median baseline PSA > 100 ng/mL exhibited a significant influence on heterogeneity, with an estimate of -0.54 and a *p*-value of 0.04. Notably, higher baseline PSA levels were associated with decreased variability across studies. The number of [^{225}Ac]Ac-PSMA cycles, baseline ECOG performance status > 1, and prior [^{177}Lu]Lu-PSMA therapy demonstrated non-significant trends towards reduced heterogeneity. [^{225}Ac]Ac-PSMA dose, median age, prechemotherapy status, elevated baseline alkaline phosphatase, and visceral metastasis showed non-significant positive associations with heterogeneity (Table 4).

Table 4. Results of meta-regression analysis. ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; PSA, Prostate-specific antigen; PSMA, Prostate-specific membrane antigen

Variable	Estimate	Stan-dard Error	Z	*p*-value
Median Baseline PSA>100 ng/mL	-0.54	0.29	-1.88	0.04
Elevated Median ALP	0.11	0.29	0.39	0.69
Taxane Chemotherapy Pretreatment	0.0002	0.006	0.04	0.96
Baseline ECOG>1	-0.012	0.35	-0.34	0.73
Median Age at presentation	0.02	0.03	0.87	0.38
Number of [^{225}Ac]Ac-PSMA Cycles	-0.004	0.003	-1.29	0.19
Prior [^{177}Lu]Lu-PSMA Therapy	-0.007	0.005	-1.25	0.212
[^{225}Ac]Ac-PSMA Dose	0.28	0.19	1.36	0.18
Visceral Metastasis	0.02	0.016	1.54	0.12
Between-study Heterogeneity				
Variable	Category	Pooled xero-stomia rate	Heterogeneity I2 (%)	*p*-value
Median Baseline PSA	>100 ng/mL	0.77	95.2%	0.0001
	<100 ng/mL	0.97	0%	

Publication bias

Publication bias assessment for xerostomia grades utilized Doi plots and LFK index tests. Minor asymmetries were detected in studies reporting any-grade and grade 1–2 xerostomia for [^{225}Ac]Ac-PSMA monotherapy, with LFK indices exceeding 1.7 (Fig. 4a, b). Trim-and-fill analysis for these grades necessitated no adjustments. Visual inspection revealed no significant bias for grade 3 xerostomia studies in [^{225}Ac]Ac-PSMA monotherapy (Fig. 4c). Studies reporting therapy discontinuation due to monotherapy-induced xerostomia exhibited major asymmetry with LFK index of 5.1 (Fig. 4d). Trim-and-fill analysis indicated overestimation, imputing two missing studies and adjusting the pooled proportion from 5 to 3% (Table 5).

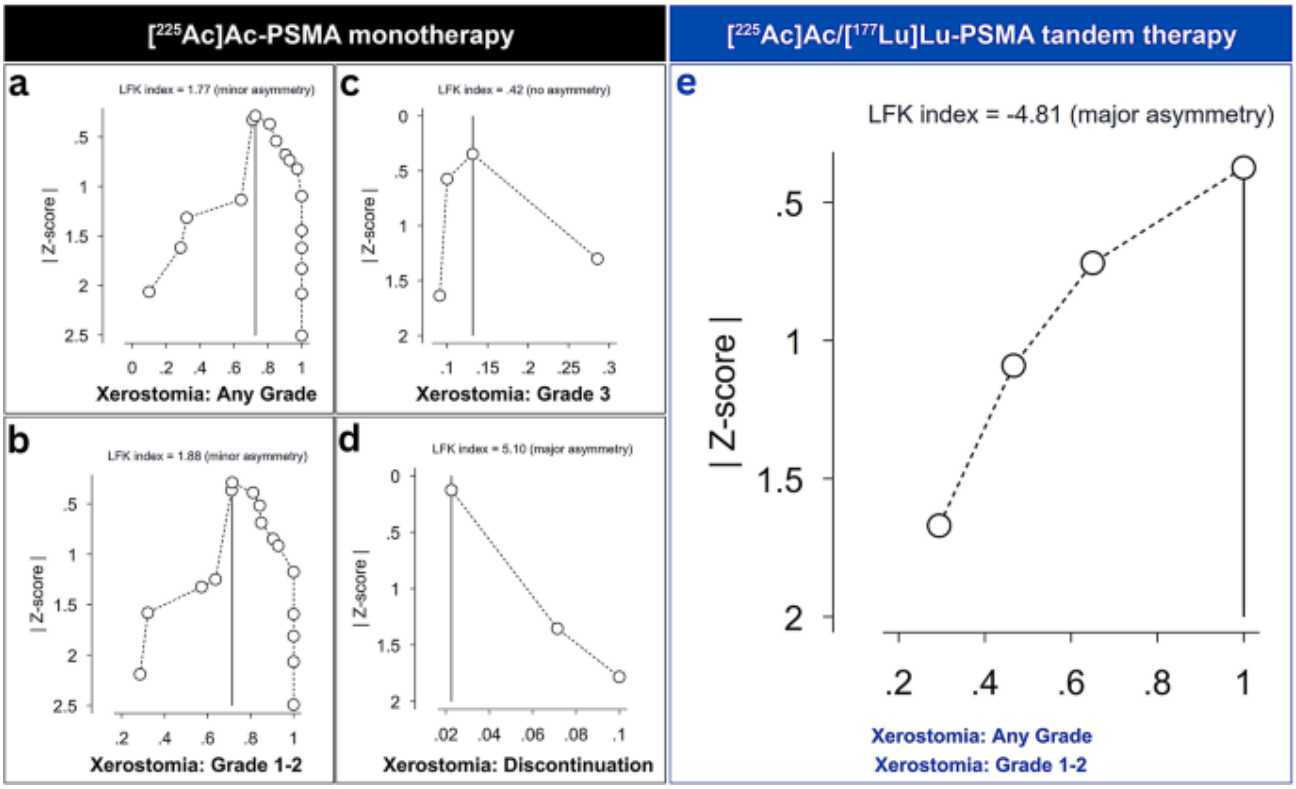

Fig. 4. Doi plots for publication bias. For [^{225}Ac]Ac-PSMA Monotherapy: (**a, b**) Minor asymmetry for xerostomia any grade and grade 1–2 is demonstrated; (**c**) grade 3 xerostomia plot shows no asymmetry; (**d**) major asymmetry in therapy discontinuation studies (LFK index 5.1) indicates overestimation. [^{225}Ac]Ac/[^{177}Lu]Lu-PSMA Tandem Protocol: (**e**) Major asymmetry in xerostomia (any grade or grade 1–2) with LFK index − 4.8 suggests underestimation of pooled proportion

For [^{225}Ac]Ac/[^{177}Lu]Lu-PSMA tandem therapy, major asymmetry was observed for any-grade and grade 1–2 xerostomia with LFK index of 4.81 (Fig. 4e). Trim-and-fill analysis suggested underestimation, imputing two missing studies and adjusting the pooled proportion from 68 to 75% (Table 5).

Table 5. Results of trim-and-fill analysis

[^{225}Ac]Ac-PSMA Monotherapy				
Meta-analysis	Studies	Missing Studies	ES (95% CI)	Adjusted ES (95% CI)
Xerostomia: Any Grade	17	0	0.81 (0.67-92)	0.81 (0.67-92)
Xerostomia: Grade 1–2	17	0	0.81 (0.68-91)	0.81 (0.68-91)
Xerosto-mia: Therapy Discontinuation	3	2	0.05 (0-0.13)	0.03 (0-0.10)
[^{225}Ac]Ac/[^{177}Lu]Lu-PSMA Tandem Protocol				
Meta-analysis	Studies	Missing Studies	ES (95% CI)	Adjusted ES (95% CI)
Xerostomia: Any Grade	4	2	0.68 (0.17-1)	0.75 (0.51-1)
Xerostomia: Grade 1–2				

Discussion

This study represents the first systematic review and meta-analysis specifically focusing on xerostomia induced by [^{225}Ac]Ac-PSMA therapy, whether administered as monotherapy or in a tandem protocol. Our results indicate the presence of xerostomia in all included studies, demonstrating its prevalence and clinical significance. Overall, xerostomia rates were found to be up to 84% in the monotherapy group. This included both grade 1–2 xerostomia, which exceeded 80% in its pooled proportion, and high-grade (grade 3) xerostomia, with a pooled proportion of 13%. Therapy discontinuation due to xerostomia was minimal, with a pooled proportion of 5%. This suggests that the high prevalence of low-grade xerostomia does not impose a life-limiting burden to the extent that it affects patients' compliance with [^{225}Ac]Ac-PSMA therapy.

Our meta-regression analysis revealed that baseline PSA values may predict xerostomia occurrence. Study cohorts with a median baseline PSA value exceeding 100 ng/mL demonstrated a significantly lower pooled xerostomia rate of 77% compared to those with median baseline PSA values below 100 ng/mL, which had a pooled xerostomia rate of 97%. This factor substantially influenced the observed overall heterogeneity. The observed inverse relationship between baseline PSA levels and xerostomia rates in [^{225}Ac]Ac-PSMA therapy merits further exploration. Higher PSA values (> 100 ng/mL) correlating with lower xerostomia rates may be attributed to increased tumor burden acting as a "sink" for PSMA-ligands, potentially reducing salivary gland uptake [46]. Conversely, lower PSA levels in dedifferentiated mCRPC might indicate reduced PSMA expression, altering ligand distribution patterns [47]. This phenomenon could potentially impact treatment efficacy and toxicity profiles, necessitating personalized dosing strategies. Mader et al. conducted a retrospective study involving 26 mCRPC patients who had completed the standard six cycles of [^{177}Lu]Lu-PSMA-617 therapy and were subsequently offered additional treatment cycles due to high residual tumor burden [48]. Upon examination of the safety profile in the included cohort, the

authors observed no grade 3 xerostomia. Grade 1 or 2 xerostomia occurred in 23% of patients during extended therapy protocol, after a median of 10 cycles (interquartile range of 7–12), supporting tumor sink effect considerations [48]. To date, studies focusing on the examination of predictive factors for [^{225}Ac]Ac-PSMA-induced xerostomia are lacking. Therefore, future research should prioritize identifying potential predictive factors that can prospectively help identify patients at high risk for xerostomia.

Notably, the adoption of a [^{225}Ac]Ac/[^{177}Lu]Lu-PSMA tandem protocol resulted in a lower pooled xerostomia rate of 68%, all of which were grade 1 or 2. This indicates that, as of the date of this meta-analysis, the tandem therapy protocol may spare patients from grade 3 xerostomia toxicity. Moreover, it has shown higher compliance rates with no recorded patient dropouts. Comparatively, adoption of the tandem protocol can result in a twofold decrease in the risk of xerostomia of any grade when offered instead of monotherapy. This is primarily because patients receive approximately half the dose of [^{225}Ac]Ac-PSMA compared to those in the monotherapy protocol.

In 2020, Khreish et al. were the first to incorporate [^{225}Ac]Ac-PSMA and [^{177}Lu]Lu-PSMA-617 simultaneously in a tandem therapy protocol [30]. A median [^{225}Ac]Ac-PSMA dose of 60 KBq/kg was co-administered alongside a fixed 6 GBq [^{177}Lu]Lu-PSMA-617 dose. The [^{225}Ac]Ac-PSMA dose was substantially lower than that offered in the monotherapy setting, which typically exceeds 100 KBq/kg. This combined therapy approach resulted in an 80% response rate and 65% grade 1–2 xerostomia rates, with 100% compliance and zero incidence of grade 3 xerostomia [30]. These compelling results have stimulated further research studies from other groups [33,34,35]. Currently, evidence is limited by the small number of studies conducted to date, all of which are retrospective in design, necessitating further large-scale and prospective evidence to establish generalizability and consolidation.

More recently, a [^{225}Ac]Ac-PSMA monotherapy de-escalation approach was employed to determine whether this would result in better compliance and spare patients from high-grade xerostomia [33]. Rathke et al. enrolled 104 patients to receive de-escalated [^{225}Ac]Ac-PSMA monotherapy. Initially, all patients received a dose of 100 KBq/kg unless skeletal superscan was evident on PSMA positron emission tomography/computed tomography (PET/CT), in which case the dose was reduced to 75 KBq/kg. Dynamic de-escalation was followed subsequently, including 2–4 MBq dose reductions in subsequent cycles depending on PSA and clinical response. This approach resulted in overall satisfactory PSA decline in 58% of patients, 100% grade 1–2 xerostomia, and 100% xerostomia-specific compliance rate. Importantly, this treatment strategy spared patients from grade 3 xerostomia [33]. Currently, we could not perform a separate analysis for this treatment approach as the aforementioned study is the only one to explore the potential benefit of the de-escalation strategy. Nonetheless, evidence from this group seems compelling enough to stimulate further research with a similar approach.

In the setting of [^{177}Lu]Lu-PSMA-617 refractoriness, another potential substitute for [^{225}Ac]Ac-PSMA is the adoption of [^{161}Tb]Tb-PSMA [49]. [^{161}Tb]Tb-PSMA has recently emerged in theranostic practice for mCRPC, offering similar physical characteristics to [^{177}Lu]Lu-PSMA-617 with a higher abundance of Auger electrons that can potentially eradicate micrometastatic deposits [50]. As described by Al-Ibraheem et al. [51], [^{161}Tb]Tb-PSMA has the potential for improved tumor targeting and reduced salivary gland uptake. The agent can also be co-administered with [^{177}Lu]Lu-PSMA-617 as dual radionuclide therapy to offer a potential synergistic effect, as previously reported [52]. Currently, two ongoing clinical trials are being conducted to assess the efficacy and safety of [^{161}Tb]Tb-PSMA therapy (NCT

NCT04833517, NCT05521412). Although clinical evidence is still developing, a recent systematic review has indicated that [^{161}Tb]Tb-PSMA can be effective in heavily pretreated mCRPC patients, including those who have previously undergone treatment with [^{177}Lu]Lu-PSMA therapy [50]. However, further confirmation is necessary, as we await the results of ongoing clinical trials (NCT NCT04833517, NCT05521412).

Several studies have investigated various methods to mitigate xerostomia induced by [^{225}Ac]Ac-PSMA therapy for prostate cancer, but a consensus on the most effective approach has not yet been reached. Strategies explored include sialendoscopy with dilatation, saline irrigation, and steroid injections [53]; external cooling of the salivary glands [19]; and the use of salivary gland protectors such as folic glutamate tablets [54]. Alternatively, Mueller et al. conducted a study investigating intrasalivary gland Botulinum Toxin (BTX) injections in mCRPC patients [55]. Ten patients received incrementally increasing doses of BTX prior to PSMA RLT, with a maximum total dose of 250 units administered. The treatment was well-tolerated, with all adverse effects classified as non-serious. All patients experienced mild pain at injection site. The most frequent BTX-related side effect was mild xerostomia. Two patients suffered from pre-existing grade 2 xerostomia due to prior therapies. Four out of the enrolled ten patients completed two [^{225}Ac]Ac-PSMA therapy cycles. Combined provoked and unprovoked salivary production 4–5 months post-initial BTX injection resulted in a mean 29% reduction in saliva production, compared to approximately 60–70% reduction following two cycles of unprotected [^{225}Ac]Ac-PSMA [55]. These preliminary findings provide a foundation for future investigations to incorporate BTX in salivary gland protection in established and emerging radioligand cancer therapies. However, despite these efforts, xerostomia remains a common and dose-limiting toxicity of [^{225}Ac]Ac-PSMA therapy. More research is needed to establish an effective, consensus-based approach to prevent or manage this debilitating side effect.

Our systematic review and meta-analysis has some limitations. First, the retrospective nature of most included studies could affect the reliability of the findings. Second, the focus on single-center studies predominantly from Europe limits the generalizability of the findings to broader populations. Despite these limitations, our study provides the first high-grade evidence research specifically focusing on xerostomia induced by [^{225}Ac]Ac-PSMA therapy.

Conclusion

Xerostomia is most pronounced in patients undergoing [^{225}Ac]Ac-PSMA monotherapy. The tandem approach with [^{177}Lu]Lu-PSMA has demonstrated potential to reduce xerostomia rates and improve treatment compliance. [^{225}Ac]Ac/[^{177}Lu]Lu-PSMA tandem therapy is associated with a twofold decrease in the risk of low-grade xerostomia compared to monotherapy. However, analyses of predictive factors for xerostomia occurrence are still lacking in the literature. Moreover, the majority of existing studies have retrospective designs, limiting the strength of their conclusions. Therefore, further large-scale, prospective studies are necessary to establish generalizability and consolidate these preliminary findings.

Acknowledgements

None.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Contributions

Akram Al-Ibraheem, Serin Moghrabi, and Ahmed Saad Abdlkadir participated in study conception, initial manuscript drafting, data acquisition and manuscript revision. Akram Al-Ibraheem and Ahmed Saad Abdlkadir prepared the figures and conducted relevant analyses. Akram Al-Ibraheem, and Mike Machaba Sathekge reviewed the final content of the manuscript. All authors read and approved the final manuscript.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Conflict of interest

Mike Machaba Sathekge is an editor in this journal. Akram Al-Ibraheem, Serin Moghrabi, and Ahmed Saad Abdlkadir declare that they have no conflict of interest.

Data availability

The current study data are available from the corresponding author on reasonable request.

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