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Quantification of Equivocal Findings in F18-Fluciclovine PET/CT Scans for Biochemical Recurrence of Localized Prostate Cancer

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Simple Summary: This study aims to assess the language used in radiology report impressions and to characterize the reader's confidence for lesions in various anatomic sites using F18-fluciclovine PET/CT scan reports. The radiographic interpretation in the scan reports' impression section was analyzed for lexica that radiologists used at least once to characterize a lesion of interest. The phrases were categorized into the following confidence categories: definitive (positive, negative), likely (consistent with, most likely, favors, probable), and unsure (suspicious for, concerning for, non-specific, conspicuous, compatible with, borderline, unknown). F18-fluciclovine PET/CT scans routinely result in equivocal findings, which vary by anatomic site of interest and prescan PSA level. The language utilized in these reports has not been standardized, which may result in improper cancer-directed therapies.

Abstract: PET/CT scans are being used to assess patients who have experienced biochemical failure following surgery or radiation therapy for localized prostate cancer. We aimed to evaluate the language used in report impressions and to determine the level of confidence that radiologists have when reporting on lesions in various anatomic sites. Between 2015 and 2021, 295 F18-fluciclovine PET/CT scan reports were identified. Thirteen phrases commonly used by radiologists in the report impression section to describe a lesion of interest were identified and categorized into three confidence categories: definitive (positive and negative), likely (consistent with, most likely, favors, probable), and unsure (suspicious for, concerning for, non-specific, conspicuous, compatible with, borderline, unknown). The use of definitive language varied depending on the anatomic site, with the highest use in bone (87.1%) and the lowest use in the intact prostate (34.6%). In patients with a PSA < 0.5, there was the highest degree of definitive certainty (89.2%), whereas in patients with a PSA > 1, there was the least definitive certainty (66.2%). The language used in these reports has not been standardized, with definitive, likely, and unsure findings reported in 68.6%, 9.7%, and 21.7% of scans, respectively.

Keywords: PET/CT; localized prostate cancer; PSA; imaging interpretation; equivocal findings

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1. Introduction

In the past 60 years, positron emission tomography (PET) has vastly advanced as a non-invasive clinical imaging modality. The spatial resolution and sensitivity of high-performance PET equipment have increased by factors of 10 and 40, respectively, compared to initial models from the 1970s [1]. PET is now combined with computed tomography (CT) in multimodal configurations for whole-body scans that can be acquired in under 10 min, which are broadly utilized for medical purposes. Widespread applications of PET/CT scans include oncologic assessment with cancer staging, evaluation of response to treatment, and diagnosis of recurrent or residual tumors.

In prostate cancer, next-generation PET/CT scans are increasingly being utilized for primary and recurrent disease staging, which can influence clinical management [2,3]. Prostate cancer patients who undergo definitive surgery or radiotherapy have a 30–50%

chance of developing a biochemical recurrence within 8–10 years of treatment, depending upon pretreatment clinicopathological features [4,5]. Recurrence evaluations have traditionally relied on CT and technetium bone scan imaging, which have a 14% and 9.4% probability of detecting cancer within three years of biochemical failure [6]. In order to assess tumor metabolism and detect small nodal and bony metastasis that may be undetectable by conventional imaging, PET tracers other than ^{18}F-fluorodeoxyglucose have been developed [7,8]. ^{18}F-Fluciclovine, a synthetic isoleucine analog with improved accuracy for whole-body staging, is FDA-approved for identifying prostate cancer recurrence in patients with elevated PSA. Its use in informing radiation planning has significantly decreased the probability of biochemical recurrence or persistence in patients undergoing salvage radiation therapy after prostatectomy [9,10]. Likewise, it can detect metastatic lesions in patients with castration-resistant prostate cancer who have had conventional imaging that was negative [11]. Studies have also shown that radiotherapy decisions were altered in 40.5% of postprostatectomy patients upon integrating PET interpretations. Furthermore, most treatment management changes involved a new treatment modality, underscoring the influential nature of these scans [12,13].

When describing "positive" findings in F18-fluciclovine PET/CT radiology reports, radiologists use many terms and phrases, reflecting an extensive range of confidence. Equivocal lesions in the oncological context are ones for which the radiologist is unsure whether they correspond to malignant disease, as abnormalities can be artifactual or associated with transient factors such as inflammation or adverse effects. Ground truth, such as biopsy, is frequently impossible to obtain for the areas corresponding to the images. The equivocal nature of lesions contributes to the variability of the categorization process from one interpreter to another [14].

In addition, the lack of a standardized classification system to report lesions on F18-fluciclovine PET/CT scans further complicates the precise, representative, and duplicatable analyses of disease presence for patient management. The heterogeneity of language used in these reports leaves room for the misinterpretation of radiology reports by clinical providers. Clear communication and knowledge of the findings that radiologists encounter in these scans are critical to avoid misimpression and optimize treatment decision-making [15]. This study aims to assess the language used in radiology report impressions and characterize the reader's confidence regarding lesions.

2. Materials and Methods

2.1. Case Ascertainment

A total of 419 F18-fluciclovine PET/CT scan reports were gathered from the Huntsman Cancer Hospital at the University of Utah, which maintains a professionally curated and prospectively collected outcomes database. The patient cohort from which the scans were derived consisted of localized prostate cancer patients who had documented biochemical failure after an original curative intent procedure (either radical prostatectomy or radiation therapy) between 2015 and 2021. Biochemical failure was defined as a PSA > 0.2 ng/mL after radical prostatectomy, a PSA value of nadir +2 after radiation therapy, or the use of any salvage therapy following the first definitive treatment. The final analysis set included 295 reports where the prescan PSA value was known within the previous 90 days of the scan.

The radiographic interpretation in the scan reports' impression section was analyzed for lexica that radiologists used at least once to characterize a lesion of interest. Three categories were established based on the level of ambiguity inherent within the terminology, with the use of definitive language indicating the highest level of confidence by the radiologist in their interpretation of the scan, followed by likely language, and then unsure language.

2.2. Statistical Analyses

Descriptive statistics were used to determine and analyze the language categories for the following anatomic regions: bone, regional lymph nodes, prostate fossa, prostate gland/seminal vesicles, and other soft tissue. The scan reports were stratified by the prescan PSA value to evaluate the correlation between two different biomarkers for biochemical recurrence of prostate cancer: PSA and imaging results. All analyses were performed using STATA (version 15, Statacorp LLC, College Station, TX, USA).

3. Results

Thirteen total phrases were identified to be routinely used by radiologists on the PET/CT scans. These were categorized into three groups depending on the level of ambiguity in describing lesions of interest. The three categories were as follows: (1) "definitive language" for the phrases "positive or negative", (2) "likely language" for the phrases "consistent with, most likely, favors, probable", and (3) unsure language for the phrases "suspicious for, concerning for, non-specific, conspicuous, compatible with, borderline, or unknown" (Table 1).

Table 1. The categorization of 13 lexical phrases into three language categories for interpretative confidence based on the level of ambiguity regarding the lesion of interest.

Language Category	Definitive	Likely	Unsure
Lexicon	Negative Positive	Consistent with Most likely Favors Probable	Suspicious for Concerning for Non-specific Conspicuous Compatible with Borderline Unknown

Definitive language (both positive and negative) was used between 34.6% and 87.1% of the time in the scans' impression reports, depending on the anatomic context (Table 2). Lesions in the intact prostate were the least likely to be characterized by definitive language with a frequency of 34.6%, whereas bone lesions were the most likely at 87.1%. Identification of lesions within intact prostates of patients post-radiation had the greatest uncertainty for biochemical recurrence, with 42.3% of scans using unsure language to describe the lesion and 23.1% using likely language. Language characterizing all the examined sites as definitively negative occurred in 18.7% of the reports. When stratified by prescan PSA value, definitively negative language for all sites occurred 48.9%, 27.8%, and 10.8% of the time for PSA thresholds of <0.5, 0.5 to <1.0, and >1.0, respectively.

The least ambiguous use of language to characterize the lesion of interest occurred in impressions of persons with a prescan PSA < 0.5, with definitive language used in 89.2% of these scans. On the other hand, the greatest ambiguity was shown in scans of patients with a PSA > 1, which used definitive language 66.2% of the time. Overall, findings using definitive, likely, and unsure language were reported in 68.6%, 9.7%, and 21.7% of scans, respectively.

Table 2. The percent frequency of language category used by radiologists in the scan reports' impressions, depending on the anatomic context of the lesion of interest (bone, fossa, prostate, nodes, soft tissue) and the PSA level of the patient (<0.5, ≤ 0.5–1, >1) at the time of the scan. * Note: although 295 scans were evaluable, not all scans reported on all the anatomically contextual sites. Therefore, the totals for any anatomic site may not sum to the total number of scans obtained.

Location of Lesion	Bone		Fossa		Prostate		Nodes		Soft Tissue		Any Region	
	n	%	n	%	n	%	n	%	n	%	n	%
All patient scans												
Definitive (Negative)	245	83.0	169	80.5	12	15.4	163	55.3	217	73.8	291	98.7
Definitive (Positive)	12	4.1	3	1.4	15	19.2	19	6.4	11	3.7	46	15.6
Definitive (Positive or Negative)	257	87.1	172	81.9	27	34.6	182	61.7	228	77.5	294	99.7
Likely	12	4.1	8	3.8	18	23.1	34	11.5	18	6.1	73	24.8
Unsure	26	8.8	30	14.3	33	42.3	79	26.8	48	16.3	161	54.6
Total *	295	100.0	210	100.0	78	100.0	295	100.0	294	100.0	295	100.0
Scans of patients with PSA < 0.5												
Definitive (Negative)	40	88.9	38	90.5	2	100.0	33	73.3	40	88.9	45	100
Definitive (Positive)	2	4.4	0	0	0	0	0	0	0	0	2	4.4
Definitive (Positive or Negative)	42	93.3	38	90.5	2	100	33	73.3	40	88.9	45	100
Likely	1	2.2	0	0	0	0	2	4.4	0	0	3	6.7
Unsure	2	4.4	4	9.5	0	0	10	22.2	5	11.1	18	40.0
Total	45	100.0	42	100.0	2	100.0	45	100.0	45	100.0	45	100.0
Scans of patients with PSA ≤ 0.5–1												
Definitive (Negative)	33	91.6	23	76.7	2	33.3	19	52.8	27	75.0	36	100
Definitive (Positive)	1	2.8	0	0	1	16.6	3	8.3	1	2.8	5	13.9
Definitive (Positive or Negative)	34	94.4	23	76.7	3	49.9	22	60.1	28	77.8	36	100
Likely	0	0	1	3.3	0	0	1	2.8	1	2.8	3	8.3
Unsure	2	5.6	6	20.0	3	50.0	13	36.1	7	19.4	22	61.1
Total	36	100.0	30	100.0	6	100.0	36	100.0	36	100.0	36	100.0
Scans of patients with PSA > 1												
Definitive (Negative)	172	80.4	108	78.2	8	11.4	111	51.8	150	70.4	210	98.1
Definitive (Positive)	9	4.2	3	2.2	14	20.0	16	7.5	10	4.7	39	18.2
Definitive (Positive or Negative)	181	84.6	111	80.4	22	31.4	127	59.4	160	75.1	213	99.5
Likely	11	5.1	7	5.1	18	25.7	31	14.5	17	8.0	67	31.2
Unsure	22	10.3	20	14.5	30	42.9	56	26.2	36	16.9	121	56.5
Total	214	100.0	138	100.0	70	100.0	214	100.0	213	100.0	214	100.0

4. Discussion

Since the approval of the F18-fluciclovine radiotracer by the United States FDA in May of 2016, the F18-fluciclovine PET/CT has become an increasingly popular tool used by providers to assess for prostate cancer recurrence [8,16]. It has been shown that the inclusion of F18-fluciclovine PET/CT into postprostatectomy radiotherapy decision-making and planning significantly improved survival free from biochemical recurrence or persistence [9,10]. Thus, accurately and confidently identifying positive disease sites is essential to optimize salvage treatment planning and delivery.

Other imaging modalities, such as multiparametric magnetic resonance imaging (MRI), have clinical guidelines in place, known as the PI-RAD (prostate imaging reporting and data) system. The PI-RADS promotes global standardization and improved risk stratification by adding a measure of confidence in the interpretation and reporting of MRI results for prostate cancer. Although the PI-RADS does not address the detection of biochemical recurrence, the similar creation of a unified system for PET/CT interpretation would improve and standardize communication between physicians [17].

Recently, PSMA PET/CT scans have also been approved for imaging patients with biochemical recurrence of prostate cancer. Like F18-fluciclovine scans, PSMA scans can be used to assist in the diagnosis and staging of men with prostate cancer. For example, PSMA scans have been proposed to help target biopsies and are routinely used for staging and detection of recurrence [8,18–21]. A PSMA-RADS scoring system has been

proposed, which aims to better classify these imaging findings into a likelihood of being malignant or benign. The system ranges from a score of 1 (considered benign) to a score of 5 (considered certain) [20,22]. In one of the only papers that compared PSMA-RADS to a reference standard (persisting PSA after radical prostatectomy), there were 15 bone lesions suspected on imaging in 406 patients scanned at initial diagnosis. Of those, only 2 of 13 lesions with a PSMA-RADS score of 3 were validated as actual metastases, and 2 of 2 lesions with a score of 4 or higher were validated [21]. An alternative categorization to PSMA-RADs, PROstate cancer Molecular Imaging Standardized Evaluation (PROMISE) has been proposed. PROMISE is a structured reporting guideline that aims to standardize the interpretation and reporting of PSMA PET/CT, which serves as a comprehensive framework to enhance consistency, accuracy, and clinical relevance in the evaluation of PSMA PET/CT images [19]. Although this categorization standard was proposed for PSMA scans, it has demonstrated utility when adapted to F18-fluciclovine scans as well [23].

Without a standardized system in place for reporting F18-fluciclovine PET/CT findings, radiologists use an array of terminology that reflect differing degrees of confidence. We found that as PSA increased, the rate of equivocal language used in F18-fluciclovine PET/CT reports increased across all the five anatomic sites studied. At lower PSA ranges, scans were more likely to be read as definitively negative. The increased probability of an ^{18}F-fluciclovine PET/CT (F18-fluciclovine PET/CT) scan being positive for biochemical recurrence is also directly associated with increases in a patient's PSA [22].

While there is a high degree of confidence for definitive certainty associated with "positive" and "negative" reads, the degree of confidence that indeterminate reads convey is unclear. Further research on the specific connotations associated with each of the lexicons identified is warranted, as individuals may have different interpretations of each word. The language categories we have established here are limited as they are based on the subjective interpretation of ambiguity.

5. Conclusions

F18-Fluciclovine PET/CT scans routinely result in equivocal findings, which vary by anatomic site of interest and prescan PSA level. The language utilized in these reports has not been standardized. Future work aims to evaluate how the proposed PSMA-RADS system correlates to these F18-fluciclovine scans once we have sufficient additional follow-up to compare to a demonstrable reference standard of truth. If the PSMA-RADS system does not correlate well to reference standards in these patients, we aim to create a clear confidence level lexicon standard to assist radiologists and providers in reporting standardization. This dataset can serve as a useful tool for improving standardization and reporting.

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