Delineating biochemical failure with 68Ga-PSMA-PET following definitive external beam radiation treatment for prostate cancer

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Abstract

Background and purpose: We investigated the role of 68Ga-PSMA-PET (PSMA) to determine the location of disease recurrence in those with a rising PSA following definitive external beam radiation treatment (EBRT).

Materials and methods: 538 men were treated with image guided EBRT to a dose of 78 or 82 Gy between 2007 and 2014. Patients at least 24 months post EBRT with biochemical failure (nadir + 2) underwent PSMA scanning. Local recurrence (LR) was defined as increased uptake within the prostate or seminal vesicles. Distant disease included lymph node (LN), bone or visceral metastases.

Results: 419 men formed the study cohort. Median follow-up was 50 months, 70 patients (17%) had biochemical failure (BF), 13 of whom have died. Of the 57 survivors, 5 had metastases detected on conventional scans; 2 were lost to follow up. 48 men (of 50 candidates) underwent PSMA; in all cases, the PSMA was unequivocally positive.

Of the 48 positive scans, 25 patients (52%) failed beyond the prostate – 5 in bones, 16 LN, 3 in both, and 1 in the lungs. Fifteen men (31%) failed within the gland and in either LN (11), bones (3), or both (1). Eight (17%) had an isolated LR, which represents 2% of patients managed with definitive EBRT and followed for at least 2 years.

Conclusions: PSMA was positive in all patients with BF. Site of failure following dose-escalated EBRT was generally distant. Isolated LR (on PSMA) occurred in only 8 of 419 patients post-EBRT.

The source of a rising PSA following definitive EBRT may be local, distant or both. This has important implications with respect to salvage versus systemic management options. In this situation, and with a PSA < 10, conventional imaging with CT and bone scan is unhelpful [1]. PSMA has a higher detection rate with a higher specificity than choline-PET [2,3], and is able to evaluate distant metastatic disease in contrast to multi-parametric MRI (mp-MRI).

Since 2015, our high risk prostate cancers have been routinely staged with PSMA; and we use PSMA to identify sites of recurrence in men post-prostatectomy, with a rising PSA above 0.2 ng/mL [4]. We have also performed PSMA in those who fail EBRT to determine sites of failure and identify those who may benefit from focal or targeted radiation treatment versus those who are best managed with observation or systemic treatment.

In this analysis, we set out to determine whether PSMA was positive in men with BF; if so, to then investigate its role to delineate sites of failure in patients who received definitive image guided and dose-escalated EBRT and who subsequently met the Phoenix definition [5] of BF (nadir + 2). Our hypothesis was that those with LR alone may have had radio-resistant disease based on bulky or hypoxic tumours predicted by factors such as PSA, T stage, dose, and higher core positivity.

Methods and materials

Study cohort

All patients at our centre are enrolled onto an ethics approved, prostate cancer patient database. 538 men were treated with image guided EBRT to a dose greater than 78 Gy between 2007 and 2014. For this study, we identified 419 patients treated to at least 78 Gy and followed for at least 24 months post completion of EBRT. Men with BF (n = 70), and without evident disease on...
conventional imaging (CT or bone scan), underwent PSMA scanning, which became clinically available in October 2014.

Scan acquisition

The \(^{68}\)Ga-PSMA radiotracer was produced on-site with a GLP (good local practice) compliant procedure using an automated radio-pharmacy cassette. Radio pharmacy quality control was undertaken using a high pressure liquid chromatography method. The patients were injected intravenously with an average dose of 2.0 M bq/kg (0.054 m Ci/kg) \(^{68}\)Ga-PSMA. All men were scanned a minimum of 60 min following injection from vertex to knees.

Image interpretation

PET/CT images were interpreted both subjectively and semi-quantitatively by experienced nuclear medicine physicians (LE, BH, EH and GS). Each lesion identified was individually evaluated as equivocal/positive or definitively positive, in addition to a semi-quantitative analysis of lesion intensity with a standardized uptake value (SUV max). Anatomical site was assigned according to a pre-coded form. Local recurrence (LR) was defined as increased uptake (SUV > 3.3) \(^{6}\), and felt to be ‘definitely abnormal’ by the imaging investigators within the prostate or seminal vesicles. Distant disease included lymph nodes (LN), bone or visceral disease, again, delineated by PSMA, and only including those findings felt to be ‘definitely abnormal’ by the imaging investigators. ‘Equivocal’ or ‘probably abnormal’ findings were not to be included in the analysis.

Statistical analysis

For purposes of comparison, patients were coded as either BF or none. Patients with BF were then further coded according to their PSMA results as local failure, distant failure or both.

Simple descriptive statistics were used in this report. Follow up was calculated from completion of EBRT for all patients regardless of whether or not they received androgen deprivation (AD). For patients who failed, the association between disease risk factors (Gleason score, iPSA, T stage, positive cores, maximum cores, risk group, hormone use, and PTV HD mean dose) and the location of the failure were tested using Fisher’s Exact test. Significant associations were further examined using odds ratios. Analysis was undertaken with IBM SPSS Statistics.

Results

There were 419 eligible patients, with a median follow up of 50 months. Table 1 delineates sites of failure based on PSMA scan according to baseline tumour risk factors. The 349 men treated with EBRT, without BF, were used as a comparator group.

The bulk of our patients were evenly split between men with intermediate or high risk disease categories \(^{7}\). Just over half the patients were managed with EBRT alone. Short term (4–6 months) and adjuvant (18–24 months) AD were each used in addition to EBRT in about a quarter of our population. The median pre-treatment PSA was 10 ng/mL (range 1–145). 122 patients were treated to a dose of 78 Gy; 297 received 82 Gy. Radiation fields included the prostate and seminal vesicles, with a margin expansion from CTV to PTV of 7 mm; except posteriorly, where it was 5 mm. The proportion of seminal vesicles treated depended on the risk of involvement. Where pelvic lymphatics were treated, the superior field border was at the L5/S1 interspace.

Seventy of 419 men (17%) met the Phoenix definition of BF, thirteen of whom have died – 7 due to prostate cancer, 4 from other and 2 of unknown causes. Of the 57 survivors, 5 had distant metastases detected on either CT or bone scans and 2 were lost to follow up. 48 of the 50 remaining men (96%) with BF underwent PSMA as per our study intent. In all 48 patients, the PSMA was reported as “unequivocally positive”.

Amongst these 48 men with positive scans, 25 patients (52%) failed beyond the prostate or seminal vesicles – 5/25 in bones, 16/25 in LN, 3/25 in both, and 1/25 in the lungs (biopsy proven mixed ductal/acinar histology). Fifteen men (31%) failed both locally and in either LN (11/15), bones (3/15), or all three (1/15). Isolated local recurrence as defined by PSMA was a rare event in our cohort. There were 8 local only recurrences, compared to 15 local and distant, and 25 distant only recurrences. Isolated local disease represented 17% of those with BF, but as a proportion of the study cohort (n = 419), occurred in only 2%. Sites of failure are further detailed in Table 2.

Overall, the only predictive factors for BF included GS8-10 disease (17% vs 9%) (\(p = 0.011\)) and initial PSA greater than 10 (16% vs 8%) (\(p = 0.04\)).

The median PSA level at the time of PSMA scanning was 5 ng/mL, ranging from 2.04 to 39 ng/mL. The median interval from BF to PSMA was 3 months (range 1–57 months).

In testing the association between location of failure and disease risk factors, those who did not fail were excluded. For the patients with BF, there was a significant association between the location of the failure and mean dose (\(p = 0.0008\)). Those who were treated with a high dose (>80 Gy) had a significantly higher odds of distant failure compared to local failure, than those treated with a low dose (<80 Gy) (OR 34.5, 95% CI 3.9, 297.99). There was no significant association between the location of the failure and the other disease risk factors (\(p > 0.05\) for Gleason score, iPSA, T stage, positive cores, maximum cores, risk group, and hormone use).

Temporal differences in the 3 groups were apparent as the median time to BF for those with distant, or distant and local disease was 39 months, versus 58 months for isolated LR. However these curves overlapped and the differences were not statistically significant.

Discussion

Previously, standard management for men with a biochemical recurrence following definitive irradiation has been to observe until distant disease declares itself or the PSA rises to a level or at a rate that warrants commencement of AD. The challenge for the radiation oncologist has been to determine whether the source of the rising PSA is persistent local disease, distant metastases, or both.

The reason for this is that diagnosing a local recurrence is notoriously difficult. Diagnosing a local recurrence via digital rectal examination is subjective and unreliable. Non-functional pelvic MRI is sub-optimal in identifying a local recurrence if the PSA is less than 10 \(^{8}\), and is not routinely performed for a biochemical recurrence. The interpretation of biopsy following EBRT may be associated with a high false positive rate and requires an experienced pathologist \(^{9}\); in addition, there is no consensus as to the appropriate timing of biopsy. Furthermore, local recurrence on biopsy does not exclude regional or distant disease.

Recently 68-Ga-PSMA-PET has demonstrated a much higher sensitivity and specificity for the detection of prostate cancer compared to traditional imaging modalities. In particular PSMA scanning has a very high specificity meaning that a positive scan is highly likely to be a true indication of disease. van Leeuwen et al. \(^{10}\) demonstrated a specificity of 95% in a series of 30 patients undergoing extended lymph node dissection and radical prostatectomy following a staging PSMA scan. In a recent meta-analysis \(^{11}\) involving 1309 patients in 16 studies, a specificity rate of
and local recurrence and only 17% had an isolated local recurrence. The positive scans (52%) had distant disease alone, 31% had distant disease and local disease (biopsy proven in 2 of 3) only disease (biopsy proven in 2 of 3). Finally, for those with recurrence confined to the prostate alone, local salvage therapies may be considered. Given the morbidity of whole gland salvage, be it surgery, to the prostate alone, local salvage therapies may be considered.

An isolated local recurrence rate of 2% overall (8 patients out of original 419 patients) bears testimony to the effectiveness of image guided and dose escalated EBRT as a treatment modality for prostate cancer.

Now that we have an accurate indicator of recurrence, we set out to delineate the patterns of failure following EBRT for all consecutive patients treated between 2007 and 2014 who met the Phoenix definition of BF with PSMA-PET. We had speculated that bulky, high PSA, low GS tumours which had received a lower treatment (SABR), or simultaneous integrated boost for PSMA-lated local disease were indeed likely to have been treated to a lower dose.

We also confirmed that the Phoenix definition is a valid tool for predicting the presence of persistent or recurrent disease as all of our patients with BF were PSMA positive. In the future, it will be interesting to see if this tracer predicts for failure at even lower levels of PSA. Although it is very speculative at present, we wonder if patterns of relapse (local only vs distant) reflect different phenotypes and whether different patterns of recurrence on PSMA scan will prove to be an early surrogate of meaningful clinical outcomes. Currently, the pragmatic utility of PSMA lies in its ability to delineate the site(s) of failure, and, to simultaneously stage the patient, rather than simply confirming the Phoenix definition. This enables more nuanced management options and allows for the deployment of emerging techniques such as stereotactic ablative radiation treatment (SABR), or simultaneous integrated boost for PSMA-PET positive sites.[12] Finally, for those with recurrence confined to the prostate alone, local salvage therapies may be considered.

97% was reported. Therefore a positive scan has the potential to significantly influence patient management as it delineates local and distant disease.[4]

In our series almost all patients with a biochemical failure (nadir + 2) who had not died or who had distant disease already declare itself on conventional imaging underwent a PSMA scan. In all cases, the PSMA was unequivocally positive. Over half of the positive scans (52%) had distant disease alone, 31% had distant and local recurrence and only 17% had an isolated local recurrence. Given the morbidity of whole gland salvage,[13] be it surgery,
brachytherapy or other modalities such as HIFU, use of PSMA, in conjunction with mp-MRI may also allow better targeting for focal salvage treatment.

We have treated 2 of our isolated local recurrences with focal (PSMA and mp-MRI defined) stereotactic radiation treatment (SBRT). As per our re-treatment protocol, both men underwent systematic prostate biopsies prior to SBRT confirming concordance between the PSMA-PET, multi-parametric MRI and the positive cores. Following SBRT, both patients have declining PSAs and have had nil toxicity to date. Two men have commenced AD, and 4 men continue to be observed.

We acknowledge that there are several limitations in this report. Plesanly, we had few BF events, and therefore even fewer isolated LR events. However, the small absolute numbers of men with BF limited our ability to further interrogate the data and demonstrate a significant relationship between percent of positive cores and/or maximum core involvement and isolated failure. Those patients treated to a lower dose were significantly more likely to have isolated local recurrence, however this may also reflect a bias in length of follow up as men who received 78 Gy were more likely to have been treated earlier on than those who received higher doses. This is also reflected in the median PSA values at time of PSMA-PET for the different sites of relapse. The relatively short follow up (median 50 months) is a limitation of this report and we intend to re-visit these data in the future with longer follow-up and more events. Another potential bias may be the fact that PSMA-PET was introduced relatively recently in the follow up of this cohort, so some men who were negative on conventional imaging after biochemical failure, were observed for some time prior to their PSMA-PET.

Another criticism of our data includes the lack of histopathological correlation in all cases following the PSMA. Pathology is often hard to obtain from non-enlarged but PSMA avid nodes. However, the treatment response was often evident clinically. For example, in those managed with SABR for oligo-metastases identified on PSMA there was a subsequent decline in PSA levels in 75% of cases. Two of our seven patients with local only failure underwent systematic biopsies that correlated exactly with the LN relapses in this report may have been marginal misses at the edge of previous pelvic nodal fields rather than true distant failure.

Conclusion

In conclusion, PSMA is a novel tracer with the ability to delineate location of disease in those with BF following definitive EBRT. Using this tracer, all patients with BF had a positive PSMA scan and we were able to demonstrate that just 2% of our cohort had isolated local recurrence. Furthermore, PSMA helps inform and target subsequent management.

Conflict of interest

None.

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References