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Prognostic Utility of PET in Prostate Cancer

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Abstract

Accurate prediction and assessment of relevant outcomes is important in clinical trial design and in clinical practice for selecting and sequencing appropriate individualized management of patients with prostate cancer. There have been many standard non-imaging based prediction tools for the various phases of prostate cancer. However these tools may be limited in individual cases and need updating based on the improved understanding of the underlying complex biology of the disease and the emergence of the novel targeted molecular imaging methods. A new platform of automated predictive tools that combine the independent molecular, imaging, and clinical information can contribute significantly to patient care and improve outcome. Such platform will also be of interest to regulatory agencies and payers as more emphasis is placed on supporting those interventions that have quantifiable and significant beneficial impact on patient outcome.

Keywords

Prostate; Cancer; PET; Imaging; Outcome

Prostate cancer is the second most common cancer and the sixth leading cause of cancer death in men worldwide despite wide regional variation in incidence and mortality. This variation may be due to the difference in biologic, socioeconomic and diagnostic and therapeutic practices around the world (1). In 2014, there is an estimated 233,000 new cases of prostate cancer representing 14% of all new cancer cases in the United States. The lifetime risk of a man developing prostate cancer is approximately 15% (1 in 6). The estimated deaths from prostate cancer are 29,480 accounting for about 5% of all cancer deaths (2). During 2004–2010, the percent of cases by stage of disease at the time of initial presentation were 81% localized, 12% regional, 4% distant, and 3% unknown. The 5-year relative survival for both the localized and regional stages is nearly 100% but it drops markedly to 28% in patients with metastatic disease (2).

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The natural history of disease is one of evolution from a clinically localized hormone-sensitive tumor to a castrate-resistant metastatic state (3). Imaging plays important current and emerging role in the evaluation of all the various clinical phases of this prevalent disease (4–7). Transrectal ultrasound (which may include three-dimensional, Doppler, use of contrast microbubbles, and shear wave sonoelastography techniques) is performed for guiding biopsy in men suspected of harboring prostate cancer, typically prompted by an elevated serum prostate-specific antigen level (PSA) or an abnormal digital rectal examination (8–11). However such approach in the post-PSA era has been associated with overdiagnosis of clinically insignificant tumors and overtreatment of these indolent tumors with its associated cost and morbidity (12). Conversely occasionally higher-grade tumors are missed on biopsy and therefore an opportunity for delivering appropriate therapy may be lost. Magnetic resonance imaging (MRI) with higher field strength, specialized coils, and multiparametric techniques (diffusion-weighted imaging, dynamic contrast imaging, elastography, spectroscopy) have also played an important role in the imaging evaluation of prostate cancer, which is anticipated to grow (13–20). MRI may be useful in localization of lesions amenable to targeted biopsy (in addition to standard sites for biopsy) and for lesion characterization (21). Real-time fusion of ultrasound and MR images at the time of biopsy has been demonstrated and may prove to be helpful in reducing the relatively high sampling error that is often associated with standard TRUS-guided biopsy procedure (22–25). Direct MR-guided biopsy procedures have also been shown to be feasible although the technique is currently only performed at few specialized centers (26–28).

When a diagnosis of prostate cancer is established, it is important to stage the disease accurately so that appropriate treatment can be delivered. In localized disease, the treatment with curative intent includes prostatectomy with pelvic lymph node dissection or radiation therapy. In some patients, active surveillance may also be a viable strategy. Unfortunately up to 35% of patients (or higher in select high-risk groups) may experience biochemical recurrence (PSA relapse) within a decade of primary therapy. Stratification of patients with biochemical recurrence is crucial for prescribing and sequencing appropriate treatments. Such therapies may include salvage therapy (surgery or radiation) for local recurrence and systemic therapy for metastatic disease. When men develop castrate-resistant state (defined as disease progression despite androgen deprivation), the prognosis is poor and treatment is directed toward enhancing overall survival and comfort (29–31).

There have been great recent strides in treatment of metastatic castration-resistant prostate cancer that has been fueled by improved understanding the biology of the disease (32, 33). The Food and Drug Administration (FDA) have approved these treatments since the initial approval of docetaxel in 2004 based on the results of TAX-327 and SWOG 9916 clinical trials demonstrating overall survival benefit (34, 35). The recently FDA-approved agents include, cabazitaxel (Jevtana, Sanofi-Aventis, Paris, France) approved in 2010 as a second-line taxane therapy in patents who have failed docetaxel therapy (Treatment of Hormone-Refractory Metastatic Prostate Cancer Previously Treated with a Taxane-Containing Regimen—TROPIC), vaccine therapy with sipuleucel-T (Provenge, Dendreon, Seattle, WA, USA), approved in 2010 for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer based on Immunotherapy for Prostate AdenoCarcinoma Treatment – IMPACT -- trial, the androgen synthesis inhibitor abiraterone

acetate (Zytiga, Janssen Biotech, Horsham, PA, USA) approved in 2011 for use in metastatic castration-resistant prostate cancer after docetaxel failure based on the COU-AA-301 trial, androgen receptor blockade with enzalutamide (Xtandi, Medivation, Inc. and Astellas Pharma USA, Inc.) approved in 2012 for treatment of patients with metastatic castration-resistant prostate cancer who have been previously treated with docetaxel based on the clinical trial AFFIRM, and radium-223 dichloride (Xofigo, Bayer Healthcare, Whippany, NJ) based on the Alpharadin in Symptomatic Prostate Cancer – ALSYMPCA – clinical trial (36–41).

Given the public health significance of prostate cancer and the ongoing accelerated targeted therapies, noninvasive imaging-based assessment of appropriateness for particular targeted treatments in individual patients and accurate predation of various relevant outcomes is considered clinically urgent.

Outcome Measures

Since prostate cancer is a remarkably heterogeneous disease, a personalized approach to patient care is most desired (42). However such approach will require identification of a combination of surrogate markers of disease that can portray the disease activity accurately before, during and after biologically and clinically tailored treatment. In order to achieve this worthy goal, relevant endpoints will be needed to design and conduct trials for drug development that can demonstrate the most beneficial impact on a selected patient outcome at minimal toxicity level. Such approach may become reality as further understanding of the complex underlying biology of prostate cancer develops.

There is a plethora of outcome measures that can be selected for conducting clinical trials and ultimately for clinical decision-making in order to select and sequence the most optimal management strategy to improve the selected outcome (43). In the clinical setting of prostate cancer, these outcome measures include but are not limited to time to biochemical recurrence (time to PSA progression), time to first metastasis, time to symptomatic progression, time to initiation of cytotoxic chemotherapy, time to radiographic progression, time to castrate resistance state, progression free survival (PFS), metastasis-free survival, disease-specific survival, overall survival, etc.

Even when a specific outcome measure is selected, there can be variability in inter-study design that makes comparison between the results of trials challenging. Gignac et al quantified the variability and the resultant error among phase II clinical trials of cystotoxic agents in metastatic castrate resistant prostate cancer that employed PFS as the outcome measure (44). There was heterogeneity in trial inclusion criteria and the type, timing, and frequency of disease assessment. In a simulation model, the investigators determined that there could be a significant difference between the trial detected and the true PFS that was directly related to variability in assessment schedules despite published standardization guidelines (45). Such variability hinders effective comparison of reported outcomes among clinical trials and the comparative effectiveness of drug development process.

Current Predictive tools

Predictive tools help with decision-making process for the clinician and the patients given the complex biology and clinical course of prostate cancer and the ever-changing landscape of treatment options at every phase of the natural history of the disease. The predictive tools include nomograms, propensity risk tables, artificial neural networks, and other methods (45–49). Deciphering the exact utility of these tools may seem daunting for both the treating physician and the patient.

Nomogram is a graphical diagram that uses various clinical parameters to allow prediction of an outcome that can be useful for clinical management decisions. Many such nomograms exist in public domain for a number of cancers including prostate cancer (http://www.nomogram.org/). Ross et al cataloged and evaluated the many nomograms that have been published between January 1966 and February 2000 (50). The search produced 42 published nomogarms that could be applied to various clinical phases of prostate cancer. It was interesting to note that only 18 (43%) of the nomograms had undergone validation and none had been compared to clinical judgment alone. In another study, the same group of investigators compared predictions of clinicians with prostate cancer nomograms (50). They found that although nomograms did not generally extend clinician prediction accuracy (average doctor excess error 1.4%, p=0.75), nomograms could be beneficial in certain clinical decision-making situations.

Partin and colleagues established the predictive nomogram tool in prostate cancer, which was updated in 2007 from its earlier versions in 2001 and 1997 (51–54). Partin tables use preoperative Gleason grade (which may differ from Gleason score of the surgical specimen), serum PSA level and clinical stage to predict outcome after radical prostatectomy. Despite the updated versions, which included multi-institutional dataset and accounted for the downward stage and Gleason score migration induced by PSA screening, the advantage of the newer versions over the initial version of 1997 could not be demonstrated (55). This notion suggests that extensive validation may be needed before one predictive tool is hastily adopted over others. Others have argued that the nomograms may not be generalizable to all patients (56, 57). A group of investigators used the information from 44 published prostate cancer prediction tools to devise a “cancer metagram” which incorporated 16 treatment options and 10 outcomes (cancer control, morbidity and survival). Despite limitations of non-inclusion of all available treatment options and relevant outcomes, the authors contended that the metagram could provide easily understandable evidence-based and patient-specific outcome predictability for clinically localized prostate cancer (58).

Shariat et al present an excellent critical review, including a comprehensive bibliography, of the prostate cancer predictive tools (59). They submit that prediction tools are generally more accurate at predicting risk than those assessed by the clinicians, who may be influenced by personal experiences or preferences in a setting of lack of consensus and conflicting or inconclusive data. They also list a number of criteria to evaluate these relatively numerous predictive tools. These criteria include discrimination (ability of the predictive tool to discriminate between patients with or without the outcome of interest), calibration (accuracy of prediction for the individual patient), generalizability (ability of the

predictive tool for a specific outcome in setting of differing patient characteristics), level of complexity (too complex tools may be of little utility in busy clinical practices), adjustment for competing risks (taking into account competing causes of morbidity and mortality), conditional probabilities (time-variability of individual patient's outcome), and head-to-head comparison (advantage of one predictive tool over another). The authors tabulate a number of predictions tools for prediction of prostate cancer on initial and repeat biopsy, prediction of pathologic state, prediction of biochemical recurrence before and after radical prostatectomy, prediction of biochemical recurrence after external beam radiation therapy or brachytherapy, prediction of metastatic progression, and prediction of survival and life expectancy. These investigators suggest that computational decision tool analysis may be helpful to compare the expected clinical consequences of various predictive tools in lieu of comparative randomized clinical trials which are challenging to perform given the high cost, delay in attaining conclusive results, and practical limitations imposed by statistical power. They also submit rightfully that in this perplexing situation, incorporation of the newly emerging biomarkers including imaging results can add significant direct information about the tumor, which can then enhance the model's predictive power in comparison to the traditional use of clinical and pathologic parameters.

Imaging as a Prognostic Tool

Imaging plays an important current and expanding role in the imaging evaluation of every phase of the natural history of prostate cancer (60). Given the limitations of the current prediction tools, newer biomarkers including circulating tumor cells, patient reported outcomes and imaging are of much interest for monitoring of clinical outcomes in specific groups of patients with prostate cancer (61). Overall relatively few studies have investigated the impact of imaging on patient outcome. This is partly due to the challenges that are associated with directly linking the results of an imaging study to an outcome given that many intervening events often occur that can also affect the outcome.

Bone scintigraphy has been a mainstay imaging in prostate cancer (62). It has been demonstrated that a negative bone scan is associated with longer time to biochemical relapse (63). Conversely, pretreatment percentage of the positive area on a bone scan may be an independent predictor of the disease death (relative risk ratio 2.603, P=0.0155)(64). Bone scintigraphy is typically analyzed visually. Computer-assisted quantitative assessment (bone scan index) has been attempted which can diminish inter-observer variability and aid with more robust longitudinal comparative studies (65, 66). Bone scan index captures the burden of osseous metastatic disease that has been shown to relate to outcome. Tait et al quantified the bone scan by simply counting the bone metastases in 561 men with metastatic castrate-resistant prostate cancer and correlating clinical outcome to thresholds of 1–4, 5–20 and >20 detectable bone lesions (67). Patients with higher number of bone metastases had shorter progression-free survival and overall survival. In fact simply dichotomizing patients into groups with 1–4 (oligometastatic) and >5 skeletal metastases provided significant prognostic information. In another similar research, a doubling of bone scan index was associated with a 1.9-fold increase in risk of death (68).

Positron emission tomography (PET) is a sensitive quantitative molecular imaging tool for interrogation of the underlying tumor biology. Many radiotracers have been or are currently being investigated for imaging evaluation of prostate cancer with PET including, but not limited to, 18F-FDG, 18F- and 11C-choline; 11C-acetate, 18F sodium fluoride, 16**a**-18F-fluoro-5**a**-dihydrotestosterone (18F-FDHT, targeted to the androgen receptor), anti-1-amino-3–18F-fluorocyclobutane-1-carboxylic acid (18F-FACBC, a synthetic L-leucine analog), and radiotracers targeted to the prostate-specific membrane antigen (PSMA), prostate stem cell antigen (PSCA), and gastrin-releasing peptide receptor (GRPR)(69–71). Almost all the studies to date have focused on diagnostic (detection) utility of these radiotracers (i.e. accumulation in tumor deposits and little or non-accumulation in non-tumor sites) either in comparison to defined reference standards or to other radiotracers. This is reasonable since a potentially useful radiotracer needs first to be examined with regard to its biodistribution, jn-vivo stability, pharmacokinetics and pharmacodynamics, and ultimately its competitive advantage over other rival conventional and new PET and non-PET radiotracers as well as other imaging methods. Here we review the few published studies on the 2 major PET radiotracers (i.e. FDG and 18F- or 11C-choline) that have reported specifically on the potential prognostic utility of these PET radiotracers in prostate cancer.

Few studies have examined the potential prognostic role of FDG PET/CT in prostate cancer. Oyama and colleagues from Japan investigated the prognostic value of glucose metabolism of the primary tumors in 42 patients with prostate cancer (72). The standardized uptake value (SUV) of the tumor was correlated to relapse-free survival following radical prostatectomy. Patients with tumors that displayed higher SUVs demonstrated a significantly poorer prognosis compared to those patients with tumors that showed lower SUVs. Despite this interesting result, FDG PET/CT is not expected to play a major role in the diagnosis and staging of primary prostate cancer in view of significant overlap that may occur among normal, benign, and malignant tissues. The researchers from the Memorial Sloan Kettering Cancer Center in New York tested the hypothesis that serial FDG PET (baseline and at 4 weeks and 12 weeks following chemotherapy) was useful as an outcome measure in men with metastatic castrate prostate cancer (73). The maximum standardized uptake values of up to 5 lesions were averaged (SUVmaxavg). Changes in this imaging parameter was then correlated to changes in the serum PSA with >25% PSA increase considered as progression (based on PSA Working Group Consensus Criteria Guideline). The authors noted that a >33% increase in SUVmaxavg, or the appearance of new lesions, dichotomized patients as progressors and nonprogressors. In another report from the same group of investigators, the maximum SUV of the most active lesion in 43 patients with metastatic castrate resistant prostate cancer was correlated to overall survival (74). A maximum SUV threshold of 6.1 provided discriminatory information on prognosis with median survival of 14.4 months if maximum SUV>6.1 and 32.8 months if maximum SUV<6.1 ($p=0.002$). Jadvar and colleagues from the University of Southern California in Los Angeles reported on a larger cohort of 87 patients with metastatic castrate resistant prostate cancer who underwent FDG PET/CT and were followed for prospectively for overall survival (75). PET parameters that were examined included not only the most metabolically active lesion, but also sum and average of up to 25 active lesions (including lymph nodes, bone, and soft tissue metastases). Comparison of overall survival was based

on univariate and multivariate Cox regression analyses of continuous PET parameters adjusted for relevant standard clinical parameters including age, serum PSA level, serum alkaline phosphatase level, use of pain medication, prior chemotherapy and Gleason score at initial diagnosis. The univariate analysis showed statistically significant hazard ratios of 1.01 (95% CI: 1.006–1.020, p=0.002) for the sum of the maximum SUV of lesions and 1.11 (95% CI: 1.030–1.180, p=0.010) for the most active lesion. However, in the multivariate analysis that adjusted for the potentially prognostic clinical parameters, only the sum of the maximum SUV remained significant with a hazard ratio of 1.01 (95% CI: 1.001–1.020, p=0.053). Further grouping of this parameter into quartiles showed that the patients in fourth-quartile range had a significantly poorer survival than those patients in the first-quartile range with a univariate hazard ratio of 3.8 (95% CI:1.80–7.90)(Figs. 1, 2). This and prior few studies suggest that there is indeed significant unique information provided by FDG PET/CT on the metabolic burden of disease that may be predictive of prognosis in men with metastatic castrate-resistant prostate cancer. This is an important notion that may be helpful in the objective assessment of the comparative effectiveness of various conventional and rapidly emerging treatments in this important clinical setting.

Systematic reviews with meta-analysis have summarized the diagnostic utility of 11C-choline or 18F-fluorocholine choline PET/CT in prostate cancer (76–78). Despite the general notion of most utility of radiolabeled choline in restaging of patients with biochemical relapse after local primary treatment for prostate cancer, many analytical limitations have been identified which may hinder general applicability and will need attention in future investigations (79–81).

A study reported on the comparative utility of 11C-choline PET/CT over clinical staging nomograms for preoperative staging of lymph nodes in intermediate-risk and high-risk prostate cancer (82). The authors found that although in this clinical setting, 11C-choline PET/CT demonstrated low sensitivity of 60% (at a specificity of 98%) for detection of lymph node metastases, but it performed better than clinical nomograms with equal sensitivity and better specificity.

PET with 18F-fluorocholine may have a role in predicting early progression in men with biochemical recurrence after primary treatment with curative intent. Gacci and colleagues performed a longitudinal study of 103 consecutive patents who had 2 PET/CT scans, one at baseline and one after 6 months from the baseline scan (83). The authors found that increase in serum PSA from baseline by greater than 5 ng/mL, decrease in PSA doubling time by less than 6 months, and increase in PSA velocity by greater than 6 ng/mL/month were highly associated with the outcome of progression on the follow-up PET/CT. Studies have also reported on the use of 11C-choline PET/CT on the prediction of outcome after salvage radiation therapy post radical prostatectomy (84). It is interesting that while initial tumor stage, risk profile, and serum PSA level before salvage radiation therapy were not different between responders and non-responders, a positive 11C-choline was able to predict the treatment failure cases. However, other studies have shown that the lower the serum PSA level at the beginning of salvage radiation therapy, the better the outcome after treatment and that the higher radiation doses are associated with greater PSA relapse free rates (85).

Breeuwsma et al correlated the findings on 11C-choline PET/CT with disease-specific survival in 64 men with biochemical recurrence after radical prostatectomy (86). The median serum PSA level was 1.4 ng/mL and the median follow-up was 50 months. The investigators found that disease-specific survival was significantly higher in the negative PET/CT group than the group with positive PET/CT. In another similar but more comprehensive study, the Italian investigators evaluated retrospectively the potential utility of 11C-choline PET/CT in prediction of prostate cancer-specific survival in 195 patients who presented with biochemical failure (PSA > 0.2 mg/mL during androgen deprivation therapy) following radical prostatectomy (87). The median interval after radical prostatectomy and median follow-up after 11C-choline PET/Ct were 8.9 years and 4.5 years, respectively. The median prostate cancer-specific survival in patients with positive and negative 11C-choline PET/CT was 11.2 years and 16.4 years, respectively. Moreover, patients with positive prostatic bed or pelvic/retroperitoneal lymph nodes had longer median prostate cancer-specific survival of 12.1 years in comparison to patients with bone metastases who had a shorter median prostate cancer-specific survival of 9.9 years. Nomograms were constructed using age, serum PSA level, initial Gleason score, pathologic stage, additional therapy, and results of 11C-choline PET/CT for prediction of prostate cancer-specific survival at 5, 10, and 15 years following radical prostatectomy. The longer-term prediction at 15 years tended to overestimate the survival in comparison to the shorter-term predictions at 5 and 10 years.

Kwee and colleagues from Hawaii investigated the prognostic significance of metabolically active tumor volume (MATV) as measured from 18F-fluorocholine PET/CT in 30 men with CRPC (88). The MATV was calculated using a vendor-supplied algorithm that determined the SUVmax and volume (defined as region encompassing 40% of the SUVmax) of the lesions, multiplied the SUVmax of each lesion by the lesion volume and summed over all detected lesions, and then termed net MATV. A measure of activity distribution within the lesion volume, termed total lesion activity (TLA) was also obtained by multiplying the lesion mean SUV and MATV, then summed over all lesions and termed net TLA. The authors found that both net MATV and net TLA were significantly associated with overall survival, suggesting that PET-based assessment of metastatic burden provides important prognostic information.

Conclusion

Predictive tools are key in clinical decision-making and individualized management of patients with prostate cancer. We outlined the utility and limitations of the current non-imaging based prognostic tools and then presented the published reports on the potential use of incorporating quantitative imaging data, particularly PET, in this important clinical arena.

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Key Points

- Predictive tools are key in clinical decision-making and individualized management of patients with prostate cancer.
- Current non-imaging based predictive tools may be limited in individual cases and need frequent updating.
- Novel platform of predictive tools that combine molecular, imaging, and clinical information are needed.

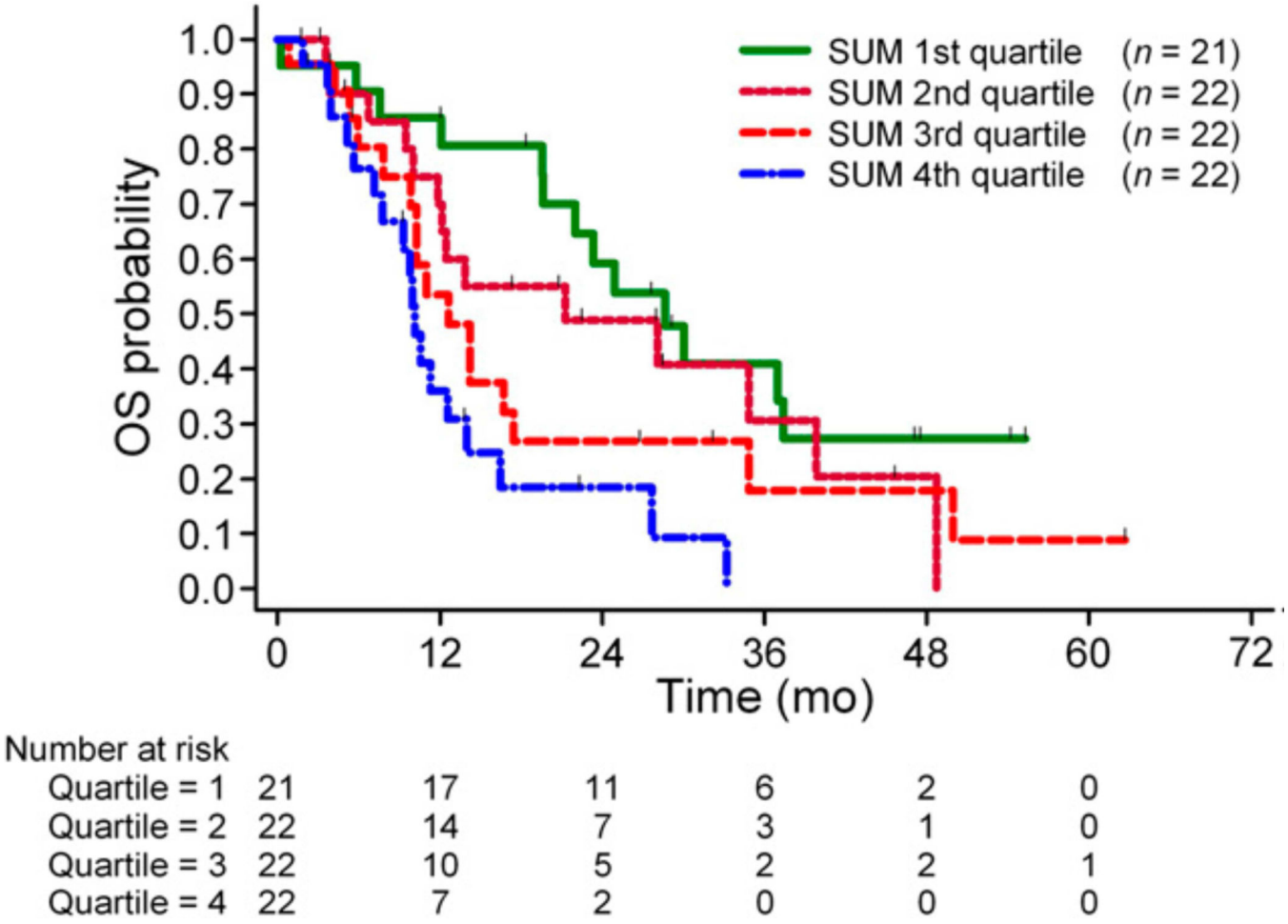

Fig. 1.

Kaplan–Meier plot of overall survival (OS) probability against sum of SUVmax (SUM) grouped into quartiles. Patients in fourth-quartile group (blue line) have significantly poorer survival probability than reference first-quartile group (green line). SUM ranges: first-quartile 0–4.6, second-quartile 4.7–13.9; third-quartile 14–28.6; fourth-quartile 28.7–217.5. From Jadvar H, Desai B, Ji L, et al. Baseline 18F-FDG PET/CT parameters as imaging biomarkers of overall survival in castrate-resistant metastatic prostate cancer. J Nucl Med 2013; 54:1195–1201, with permission.

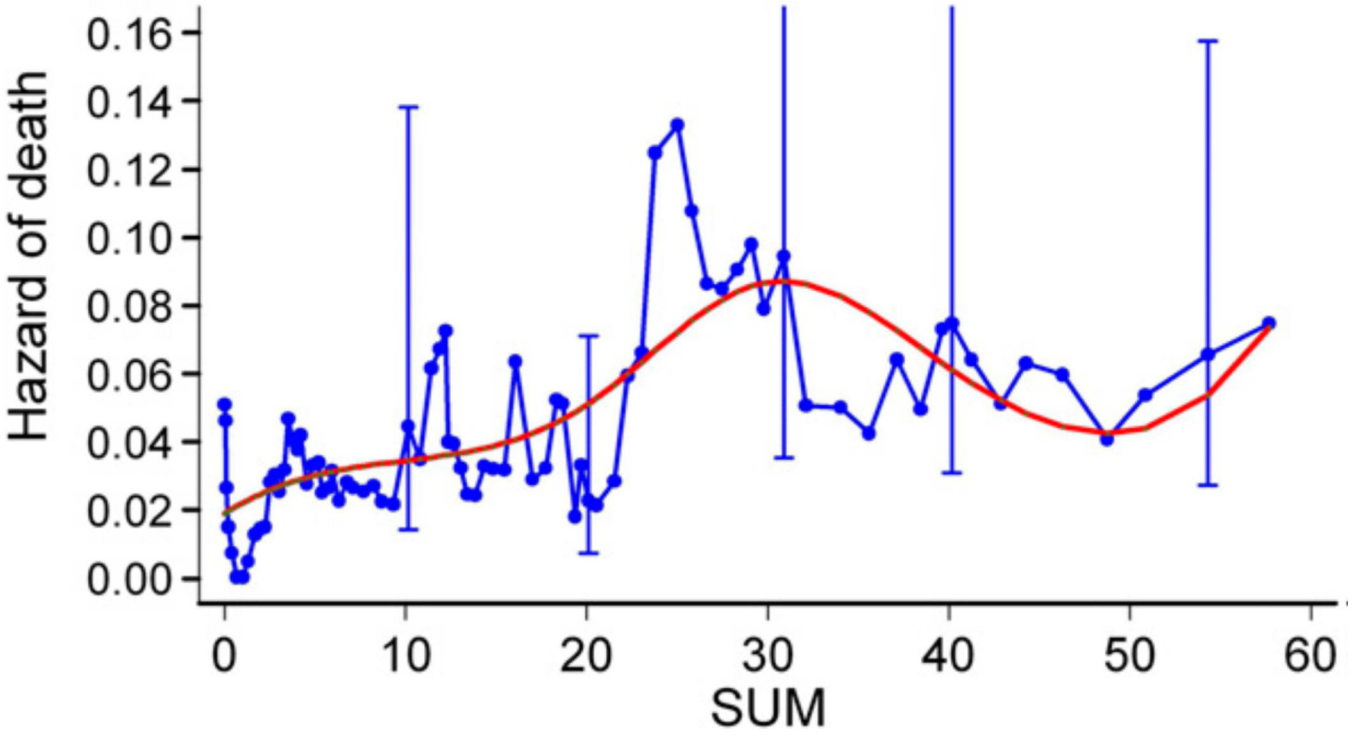

Fig. 2.

Moving hazards of death (blue line) in relation to sum of SUVmax (SUM) interpreted as chance of death per person per month; cubic spline smoothed line (red line) is superimposed. There is upward shift of curve for SUM greater than 20.

From Jadvar H, Desai B, Ji L, et al. Baseline 18F-FDG PET/CT parameters as imaging biomarkers of overall survival in castrate-resistant metastatic prostate cancer. J Nucl Med 2013; 54:1195–1201, with permission.