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Original article

Gross tumor volume and clinical target volume in prostate cancer: How do satellites relate to the index lesion

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ABSTRACT

Purpose: There is an increasing interest for dose differentiation in prostate radiotherapy. The purpose of our study was to analyze the spatial distribution of tumor satellites inside the prostate.
Methods and materials: 61 prostatectomy specimens were stained with H&E. Tumor regions were delineated by the uro-pathologist. Volumes, distances and cell densities of all delineated tumor regions were measured and further analyzed.
Results: Multifocal disease was seen in 84% of the patients. The median number of tumor foci was 3. The median distance between the index lesion and the satellites was 1.0 cm, with a maximum of 4.4 cm. The index lesions accounted for 88% of the total tumor volume. The contribution of tumor foci < 0.1 cm^3 to the total tumor volume was 2%. The median cell density of the index lesion and all satellites, regardless of size, were significantly higher than that of the prostate.
Conclusions: Satellites do not appear in a limited margin around the index lesion (GTV). Consequently, a fixed CTV margin would not effectively cover all satellites. Thus if the aim is to treat all tumor foci, the entire prostate gland should be considered CTV.
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Prostate cancer is predominantly a multifocal disease, which consists of an index (largest tumor) lesion and one or more satellites. Histopathological studies show that the mean number of tumor foci in a prostate is about 3 (range 2.24–3.92). The majority of the tumor foci are between the 0.5–1.5 cm^3 in volume and 80% of the tumors have foci in both the left and right lobe of the prostate. In almost 90% of the prostate cancer patients the total tumor volume is less than 10% of the prostate volume [1–4].

The positive predictive value of multi-parametric MRI for detecting a prostate tumor is high (80–98%) [5–12]. However, the sensitivity and specificity of detecting separate tumor foci relies to a large extent on their size and Gleason score. The sensitivity of multi-parametric MRI is significantly higher for tumors > 5 mm in diameter as well as for Gleason scores greater than 7 [7,10]. MRI has also better accuracy in predicting histopathology tumor volume in tumors larger than 0.5 cm^3 [8,11].

The current standard in radiotherapy is to treat the whole prostate gland with a homogeneous dose regardless of the stage and Gleason score. Imaging of tumor foci for target definition within the prostate gland is not common practice. This is in stark contrast to other types of cancer where radiotherapy treats the gross tumor volume (GTV) with a high dose and a clinical target volume (CTV) with a lower dose. With multi-parametric MRI for tumor detection, integrated boosting of the MRI-visible tumor is currently tested in several clinical trials e.g. FLAME, HEIGHT, TARGET trials (clinicaltrials.gov). This concept is based on tumor control probability (TCP) models assuming a relationship between the number of clonogens and tumor volume [13]. Assuming that the CTV contains only microscopic disease and thereby less tumor cells than the GTV, a lower dose to the CTV is warranted.

The rationale of focal radiotherapy in low risk prostate cancer is to reduce overtreatment, increase normal tissue sparing and thereby decreasing morbidity while still giving adequate tumor treatment. However, the success of focal radiation treatment relies heavily on adequate imaging to detect all "clinically relevant" tumor foci in the prostate.

The purpose of our study was to analyze the spatial distribution of tumor satellites in the prostate and to evaluate if this could be used to refine the GTV–CTV concept for radiotherapy treatment planning. To this end we studied distances, volumes and cell densities of satellite lesions relative to the index lesion in prostatectomy specimen.

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Methods and materials

Patient selection

A total of 61 patients with localized prostate cancer were treated with radical prostatectomy between 2010 and 2012 and gave their informed consent to store and further analyze the specimen.

Pathology

All 61 radical prostatectomy specimens were weighed, measured, inked and fixated for 24 h by formalin injection (10% formalin, 10 cc). The top and bottom of the specimen (1 cm) were sliced vertically in order to evaluate extra-prostatic extension and were not included in this study. The prostate was divided into axial slides every 4 mm (1 mm thick). A total of 296 slides were stained with hematoxylin and eosin (H&E).

On the H&E stained axial slides all tumor regions were delineated by a dedicated uro-pathologist. The delineated slides were digitized and imported into an in-house developed delineation program assuming a 4 mm distance between the slides. The tumor contours were copied in the delineation program and the shortest distance between the borders of the index lesion and the satellites were measured (Fig. 1). The volumes of all the delineated tumors were calculated. The small satellites that only captured 1 slide were calculated with the following formula: length × width × slide thickness in cm × 0.4 [14].

Cell density measurements

To further characterize the index lesion and satellites as well as normal prostate tissue, the H&E-stained slides were scanned with an Aperio ScanScope XT (Aperio Technologies Inc, Vista, CA, USA) for measurement of the cell density. All slides were scanned with a 20× objective magnification. Cell density measurements were performed with Slidepath Tissue IA 2.0 (Leica Microsystems, Wetzlar, Germany). The delineated tumor foci were marked and calculated separately after defining the threshold for the stained nuclei color definition. The same threshold was used in all slides to prevent bias. Validation was done by hand counting which showed the algorithm had an 8% miss of nuclei and a 7% count of non-existing nuclei. Because this under and over score was in balance no correction factor was used.

Statistical analysis

The Shapiro Wilk test was used to determine distribution of the data. Data were analyzed by using descriptive analysis to compute the median values and ranges, the Spearman correlation and Kruskal Wallis tests were used to analyze the statistical difference between the cell densities. The Chi-Square test linear-by-linear association was used for comparison between the different (multifocal–unifocal and bilateral–unilateral) groups.

All statistical analyses were performed using IBM-SPSS Statistics V 20 (IBM, Armonk, NY, USA).

Results

Patient characteristics are shown in Supplementary Table 1. The patients had a median age of 62.7 years (range 50–74). The median PSA level was 11 ng/mL (range 4.1–37). Most patients had a clinical stage T2 or less. More than 80% of the patients had a Gleason score 7 (3 + 4) or less at biopsy. Multifocal disease was seen in 84% of the patients ($n = 51$) and 80% ($n = 49$) had tumor foci in both the left and right lobe of the prostate.

Data on volumes, distances and cell densities were found not normally distributed by means of Shapiro–Wilk testing. The median volume of the index lesion was 1.7 cm^3 (range 0.02–12.3 cm^3) and accounted for 88% of the total tumor volume. 83% of the index lesions had a volume $\geqslant$ 0.5 cm^3. The majority of the index lesions (84%) was situated in the peripheral zone.

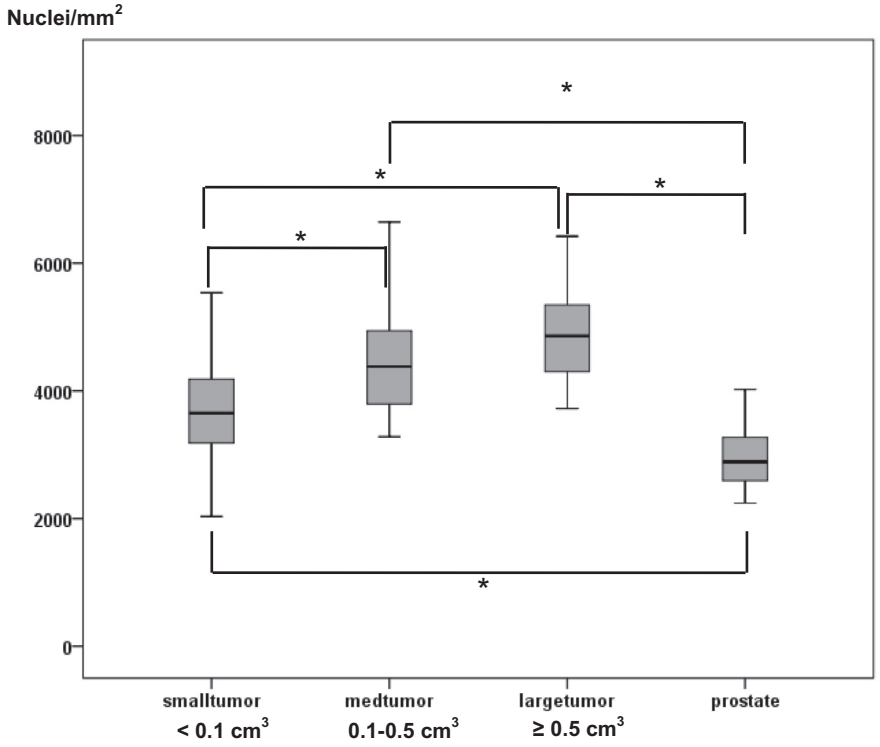

Fig. 1. Cell densities of the tumor foci divided by volumes (<0.1 cm^3, 0.1–0.5 cm^3 and $\geqslant$0.5 cm^3) and normal prostate tissue.

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