Pathology – Research and Practice 210 (2014) 312–317

Contents lists available at ScienceDirect

Pathology – Research and Practice

journal homepage: www.elsevier.com/locate/prp

Original Article

A modified point count method as a practical approach to assess the tumor volume and the percent gland involvement by prostate carcinoma

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ARTICLE INFO

Article history:
Received 11 December 2013
Received in revised form 25 January 2014
Accepted 10 February 2014

Keywords:
Prostatic neoplasms
Pathology
Prostate-specific antigen
Tumor burden

ABSTRACT

This study reports a modified point-count method for quantifying the extent of carcinoma in prostatectomy specimens ($n = 143$), as adapted from Billis et al. (2003) [3]. The prostates were studied as follows: the basal/apical margins were sampled using the cone method. The remainder of the gland was divided into 12 quadrant-shaped regions that were sampled using two slices. Eight equidistant points were marked directly on the coverslip over each fragment. The points inside the tumoral areas were counted and expressed as both the percentage of prostate gland involvement by carcinoma (PGI) and the tumor volume (TV). A significant correlation between the preoperative PSA levels and each of the three quantitative estimations were observed, with improved correlations with the PGI and TV values obtained using the point-count method (viz. number of slices involved (NSI) ($r = 0.32$), PGI ($r = 0.39$) and TV ($r = 0.44$)). With the data sets stratified into three categories, all three methods correlated with multiple parameters, including Gleason scores ≥ 7, primary Gleason scores ≥ 4, perineural/angiolymphatic invasion, extraprostatic extension, seminal vesicle invasion and positive margins. All three quantitative methods were associated with morphologic features of tumor progression. The results obtained using this modified point-count method correlate more strongly with preoperative PSA levels.

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Introduction

Prostate carcinoma has a high incidence in developed countries, with more than 643,000 new cases in 2008, representing 20% of all malignancies in males. Compared with the 70% ten-year survival rate observed by patients in developed countries, mortality rates from prostate carcinoma are asymmetrically higher in developing regions of the world [32]. In Brazil, more than 60,000 new cases were diagnosed in 2012, reflecting an annual incidence of 62/100,000 [14]. The College of American Pathologists (CAP) classifies prognostic factors in categories I (proven prognostic value and useful in daily practice), II (factors supported by preliminary experimental and clinical data, but waiting validation in large clinical studies) and III (other suggested factors). The category I prognostic factors for prostate carcinoma include pre-operative serum prostatic specific antigen (PSA) levels, Gleason grade, staging and surgical margin involvement at prostatectomy. Upon completion of the examination of a prostatectomy specimen, the relevant morphologic findings that are consequential in guiding patient treatments and follow up include the Gleason grade, extraprostatic extension, seminal vesicle invasion, positive surgical margins, intraprostatic perineural invasion, tumor volume and nodal metastasis [7].

According to a survey by the American Society of Clinical Pathologists, only 12% of pathologists use total embedding as the routine method for the examination of radical prostatectomy specimens [28]. In a recent survey, the International Society of Urologic Pathology (ISUP) made efforts to reach minimal consensus on the handling of prostatectomy specimens. Several widespread practices, such as inking margins and the cone method for the examination of both apex and base, were included in the consensus determination.

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http://dx.doi.org/10.1016/j.prp.2014.02.002
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Both the total embedding of the prostate and the use of whole mounted sections (to assure the identification of the diameter of the largest tumor focus) were not included in this consensus [23]. In the last ISUP survey, the consensus determination suggested that the pathology report of a prostatectomy specimen should include a quantitative estimate of the cancer volume, with the specific protocol decided by each laboratory. As part of this recommendation, this protocol should be well-defined and standardized for the appropriate use by all pathologists within the institution [30]. Several experts, however, explicitly recommend a reporting of the percentage of tumor involvement in all prostatic tissue specimens [12,26]. The report from the consensus conferences of ISUP recognized that a unified method to measure and report the cancer volume from a radical prostatectomy has long been a controversial issue in urologic pathology, with considerable debate on the magnitude of effort that pathologists should invest in determining the cancer volume values to be included in the pathology reports.

Tumor volume has been previously associated with decreased survival and has been included in the morphologic criteria for poor prognoses, including high grade and advanced stage diagnoses [11,13,18,20,21]. Many studies on this issue have failed to support these observations [25,30]. Several studies have been limited by the inclusion of locally advanced disease cases, while both tumor size and percentage are considered to be important measures in particular for those patients with organ confined tumors [10]. Large tumors may display indolent behaviors, remaining confined in a large prostate with concomitant nodular hyperplasia. Several studies have shown that the percentage of the gland involved by the carcinoma has prognostic value [4,17,20,22], with this factor more predictive than the tumor volume [17,20]. Recently, several authors have suggested the use of the diameter of the largest tumor focus as a morphologic feature with prognostic value [6,8]. The estimation of this factor would most likely require the use of whole mounted sections, which is the current practice used by 16% of surveyed uropathologists [23].

The authors of this present study recognize that a major step in the advancement to develop the method to quantify and report the extent of the tumor in prostatectomy specimens was presented in the proposal by Billis and colleagues [2,3]. This advancement in the protocol included several elements: (1) the basal (bladder neck) and apical margins were sectioned into cones and cut into sagittal slices; (2) the serial transverse sections of the specimen were further sliced into quadrants; (3) the tumor areas were contoured in the hematoxylin-eosin glass slides; (4) the contoured areas were manually transferred onto a sheet of paper (drawn) using quadrants containing eight equidistant points; (5) the total amount of positive points (inside the countered areas) represented an estimation of the tumor extent. This method has been adopted as a recommended method to handle radical prostatectomy specimens by the Brazilian Society of Pathology [1]. Even with the simplicity and practicality of this protocol (avoiding computer based morphometry, for instance), the point count method has not been widely adopted. The authors of this present study suggest that there are several disadvantages in the original proposal:

- transferring the drawings from glass slides to sheets of paper may not be attractive for most pathologists, as this method is time consuming;
- the pathologist who draws in the points within the quadrants may be influenced by previous observations of the points;
- the number of quadrants examined in each specimen can be variable (12–56), possibly as result of a method of obligatory total embedding;
- the results are expressed as a number of positive points, which is not an estimate that is easily understood by urologists and oncologists. Other parameters, such as either the percentage of prostate involvement by the carcinoma or the tumor volume, are universal with an obvious interpretation in a pathology report.

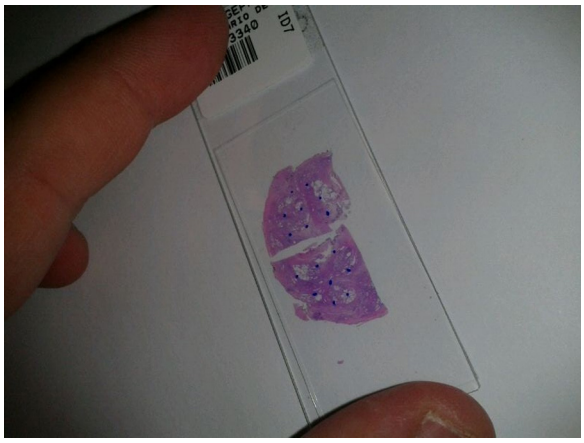

Fig. 1. The point count method. Each hematoxylin-eosin stained glass slide (containing two slices) had eight equidistant points painted directly over the fragments.

In this present report, an alternative point count method is proposed that provides improved simplicity, allowing an expression of the results as a direct estimate of either the percentage of prostate involvement by the carcinoma or the tumor volume.

Materials and methods

Patients and protocols

All consecutive radical prostatectomy specimens examined in the Laboratory of Pathology IMAGEPAT (Salvador, Brazil) from May 2010 (the date that the proposed protocol was adopted) to May 2013 were included in the study. The project was approved by the Research Ethics Committee of Centro de Pesquisas Gonçalo Moniz (CPqGM/FIOCRUZ) located in Salvador, Brazil.

All radical prostatectomy specimens were examined using the same protocol. For each specimen, the weight, measurement and volume were documented. The entire external surface was inked. Both the apical and basal margins were sectioned according to the cone method and sliced in the sagittal plane. Two sections of the proximal third of each seminal vesicle and deferent duct were processed. The remnant prostate was transversally sectioned into three thirds of equivalent thickness, representing an apical, an intermediate and a basal third. Each region was sliced into quadrants (resulting in twelve zones). Each zone was further sectioned, alternating one slice for the gross specimen archive and one slice to be processed. Two slices were processed for each region, alternating one slice (24 slices in the quadrant shape, including the circumferential margin). Each resultant hematoxylin-eosin stained glass slide (containing two slices) had eight equidistant points painted directly over the fragments (Fig. 1). The points were inserted in the same manner used in the quadrants on the sheets of paper from the original point count protocol [3]. After a microscopic examination, points that were inside the tumor area were counted. The point count was recorded from the slice with more involved points in each one of the twelve sampled regions. The microscopic report included the number of slices involved (x of 2) and the points involved (x of 8) for each one of the 12 different regions. As the number of possible points to be counted was 96, the total point count was used to approximate the percentage of gland involvement by the prostate carcinoma. The conversion of the percentage of gland involvement in the tumor volume was based on an assumption that the area fraction of a phenomenon in a solid is equivalent

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