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DEVELOPMENT OF PROSTATIC CARCINOMA

Morphometric and pathologic features of early stages

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Abstract

The natural history of prostatic adenocarcinoma has been studied in a series of 261 radical prostatectomy specimens from Stanford. Total tumor histologic grade, cancer volume, zonal distribution of the tumor and correlation with its direction of spread, capsular penetration, seminal vesicle invasion and periprostatic extension were quantitated for each case. We identified specific morphologic and histologic features for cancers which arise in the anteromedial transition zone which contains BPH nodules, and for cancers which arise in the posterolateral peripheral zone. Stage A cancers are almost equivalent to transition cancers and stage B cancers to peripheral zone cancers. Prognosis as measured by lymph node metastasis was not different between these two groups of cancers but only related to their volume of poorly differentiated areas.

Key words: Prostate cancer, pathology, natural history, radical prostatectomy, prognosis.

The natural history of prostatic adenocarcinoma is clearly reflected in the coordinated patterns of evolution of its various morphologic features. The prostate is an organ which lends itself well to the observation and quantification of such morphologic parameters as cancer location, cancer volume, intraglandular progression, pattern of spread through the capsule into the periprostatic structures and seminal vesicles, and total tumor histological grade.

In our continuing series of radical prostatectomy specimens, we have demonstrated the role of anatomic structures in local spread of prostatic carcinoma. The early progression of these carcinomas is determined by its tendency to follow tissue planes of least resistance. Then, with time, progressive loss of differentiation permits an increasing ability to grow without regards to tissue planes. The tissue planes which have been identified are perineural spaces, ejaculatory duct sheath and Denonvilliers' fascia muscular bundles. Transversely arranged fibromuscular bundles such as prostatic capsule and boundaries between histologic zones act as a barrier to the progression of well-differentiated cancers. These carcinomas penetrate the capsule along the perineural spaces, and invade the seminal vesicles along the wolffian structures.

They also tend to stay within their zone of origin, which may be either the transition zone, that anteromedial portion of the prostate which is susceptible to the development of benign prostatic hyperplasia (BPH) (Fig. 1A), or the non-transition zone which consists of the posterolateral glandular tissue (peripheral and central zones). The transition zone boundary represents the limit of the growth of this tumor.

We have evaluated the Gleason grading system in this series of radical prostatectomy specimens, using semiquantitative grading of the entire tumor together with quantitation of cancer volume and spread within the gland. Prostate cancer appears to be the most predictable human cancer and the potential of metastasis was clearly related to its volume and percentage of poorly (grade 4–5) differentiated areas. Grades 1 and 2 appeared to be related to cancer originated in the transition zone.

These results have proved useful both in improving the estimation of patient prognosis and in developing more accurate concepts of natural history of this common cancer.

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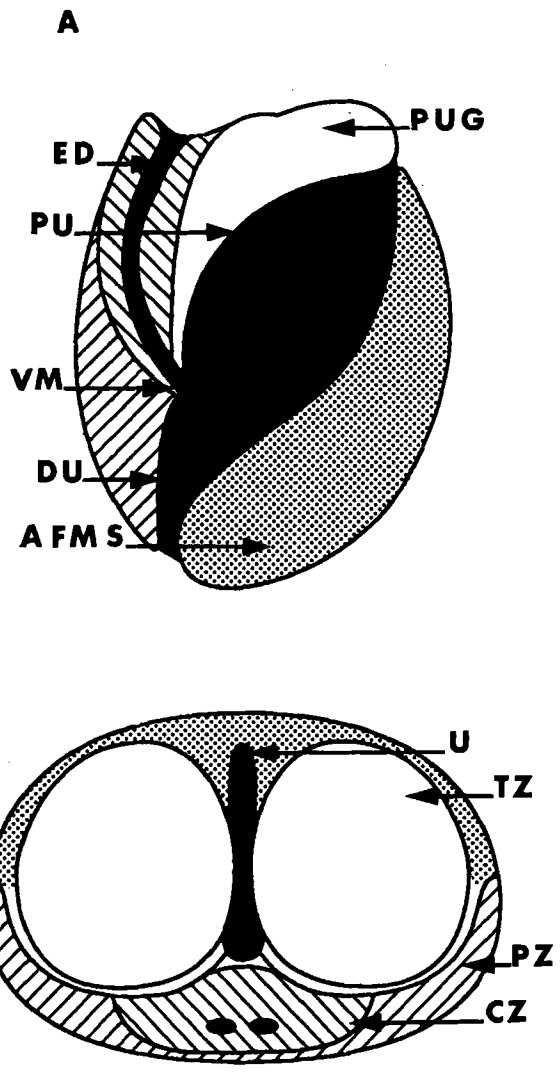

Fig. 1. Schematic representation of a 70 gm prostate. A = sagittal section, B = transverse section above veru-montanum, AFMS = anterior fibro muscular stroma, ED = ejaculatory ducts, PU = proximal urethra, DU = distal urethra, PUG = peri urethral glands (median lobe of adenoma), TZ = transition zone (lateral lobe of adenoma), PZ = peripheral zone, CZ = central zone.

Material and Methods

Cases were selected from a series of 300 radical prostatectomies performed at Stanford University Medical Center between January 1985 and March 1989. Thirty-nine cases were excluded because of prior radiation or hormonal therapy. The remaining series consisted of 261 radical retropubic prostatectomy specimens in patients ranging in age from 38 years to 79 years. Twenty-three of these cases had carcinoma metastatic to lymph nodes on permanent (histopathology) sections. In 20 of these cases, the nodes had been negative by frozen section, and the deposits were small to microscopic in extent. The remaining 3 cases had small nodal metastases on frozen section but were subjected to prostatectomy because of local obstructive problems. Demonstration of nodal metastases at frozen section is ordinarily a contraindication for prostatectomy.

Immediately following removal, each specimen of prostate with attached seminal vesicles was processed by the Stanford technique, as previously described (1). Briefly, after surface marked with dye and overnight fixation in undiluted (37%) formalin, the prostate was sectioned at 3 mm intervals in transverse planes perpendicular to the rectal surface. Seminal vesicles with vas deferens were also removed by a transverse cut taken as close as possible to the prostate base.

Then the next transverse cut, which represented prostate base with remaining seminal vesicle tissue, was taken at a thickness of 4–5 mm rather than the standard 3 mm. Thereafter this block of tissue, showing both prostate base and seminal vesicles, was serially subsectioned in vertical parasagittal planes spaced 3 mm apart.

The most distal section at the apex was cut at a thickness of 4 to 5 mm and then recut sagittaly in the same way.

Each seminal vesicle was bisected in a coronal plane. Seminal vesicle invasion was defined by the presence of malignant cells within the muscular wall or epithelium of their ducts. The percentage of the volume of each seminal vesicle invaded by tumor was assessed.

The outlines of carcinoma on all sides including in the TUR specimens in case of stage A cancer were marked in ink and transferred by tracing to a comprehensive map of the entire cancer and prostate. Cancer volume was calculated by computer planimetry. From the map and slides, the relationship of each cancer to the transition zone boundary was determined, and the tumor was classified according to whether it appeared to be of transition zone origin or non-transition zone origin, as previoulsy described (2). The percentage of the total cancer occupied by each Gleason grade and by intraductal carcinoma was estimated by careful study of all the areas of cancer on all sides.

The prostate capsule on each slide was carefully inspected microscopically for areas of complete capsule penetration of cancer through the capsule surface into periprostatic fibrofatty tissues.

Areas of penetration were precisely measured by an ink line drawn along the capsule surface on the slide (1-cm line length corresponded to 0.5 cm^2 area of capsule penetration) and transferred to the traced maps.

Perineural space invasion by prostatic carcinoma was searched, and in areas previously marked as capsule penetration, it was estimated what percentage of each area of extraprostatic cancer consisted of tumor in the perineural spaces. For each cancer, the amount of extracapsular spread that was related to perineural spaces was summed for all areas to derive a single percentage figure for each carcinoma.

Denonvilliers' fascia which covers the posterior aspect of the prostate and surrounds the wolffian structures was searched for the presence of cancer. In this study, only presence of cancer progressing within Denonvilliers' fascia at its mid portion, on each side of the midline, not related to perineural spaces, represented the definition of Denovilliers' fasica invasion. Cancer spreading at the level of the superior and inferior neurovascular pedicles to the prostate which course in the lateral portion of Denonvilliers' fasica, was quantitated in the perineural space invasion study.

Results

Cancer location and clinical staging

In a study of 243 consecutive radical prostatectomy specimens removed for 28 stage A and 215 stage B cancers, (3) it was determined for each case whether the cancer had originated in the transition or non-transition zone.

In 24 of 28 (86%) stage A cancers, tumor originated in the transition zone and in 201 of 215 (93%) stage B cancers, tumor originated in the non-transition zone.

Among the 14 stage B cancers which were found to emerge from the enlarged transition zone by BPH, 7 were larger than 12 ml in volume, and were felt at rectal examination since they invaded the peripheral zone. There were also 7 small transition zone cancers in which a posteriorly projecting BPH nodule was palpated leading to a fortuitously positive needle biopsy.

The 4 stage A cancers which originated in the non-transition zone, were large cancers having grown out of their zone to reach the transition zone area.

Study of the remaining glandular tissue on prostatectomy specimens for stage A cancers indicates that the resection margin of TUR seldom extends outside the transition zone.

Intra-prostatic spread

On a series of 88 radical prostatectomy consecutive cases (2) where the zone or origin of cancer was determined, there were 67 non-transition zone and 21 transition zone cancers.

Frequency of invasion of the transition zone boundary for these 2 groups of cancer was a function of cancer volume: 19 of 29 non-transition zone cancers less than 3.7 ml contacted the transition zone boundary, 13 were molded to this boundary and 7 penetrated in an area of this boundary.

Sixteen of 31 non-transition zone cancers larger than 3.7 ml were confined entirely within their zone and their anterior aspect was molded to the contour of the transition zone boundary; some of the 15 cancers which penetrated this boundary showed a similar partial conformity to the transition zone boundary and invasion across this boundary was limited to a portion of the cancers.

Ten of 21 transition zone cancers crossed the transition zone boundary, and most of the 21 cancers were partially or totally molded to the transition zone boundary. Only cancers less then 3.7 ml were entirely confined to the transition zone.

Histological grade, cancer volume, and distant metastasis

In Fig. 2 the mean average percentage of total cancer area (volume) occupied by each Gleason grade and intraductal carcinoma is compared between six consecutive volume ranges (4). In Fig. 3 the grade—volume relationships of Fig. 2 are diagrammed separately for 37 carcinomas of transition zone origin vs 172 non-transition zone carcinomas.

Grade 3 cancer was the dominant grade in all cancer volumes representing 76% of the total tumor in the smallest carcinomas. Grade 1 and 2 cancer represented 59% of the total tumor in the smallest tumor originated in the transition zone but less than 3% in the non-transition zone group of cancer.

Clear cells areas were noted in 87% and 38% of cases respectively in transition zone and non-transition zone cancers. However, this clear cell cancer represented more than 50% of the tumors in 63% of these cancers in the transition zone group and only 5% in the non-transition zone group.

Grade 4 cancer represented 7% of the tumors in the smallest range of volume, increasing in proportion in higher cancer volume to represent 35% in carcinomas larger than 8 ml. Grade 5 areas were seen only in tumors with grade 4 elements. Intraductal cribriform grade 3 pattern was indentified in half of carcinomas larger than 4 ml, but only 20% of cancers under 1 ml. Multivariate logistic regression analysis was applied to test the prediction of lymph node metastasis from the five histologic

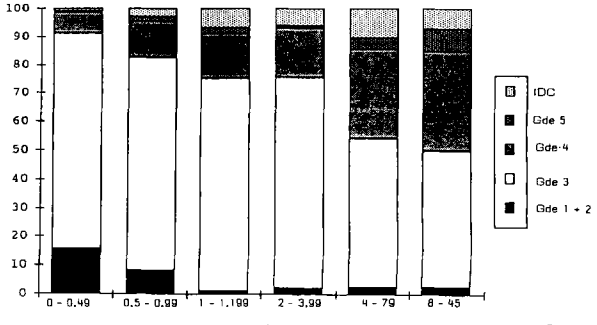

Fig. 2. Cancer volume in ml. Mean average percentage of each histologic grade and intraductal cancer (IDC) compared between cancers in 6 consecutive volume ranges. There are 21 cases under 0.5 ml in volume, 28 cases at 0.5–1.0 ml, 31 cases at 1–2 ml, 45 cases at 2–4 ml, 43 cases at 4–8 ml, and 41 cases larger than 8 ml. All 209 cases are included and volume scale is logarithmic.

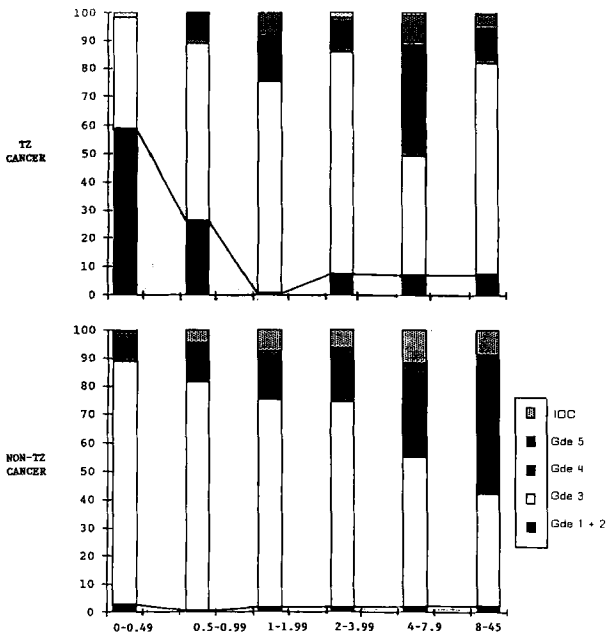

Fig. 3. Average histologic grade related to cancer volume in ml as in Fig. 1 but tabulated separately for 37 transition zone cancers vs 172 non-transition zone cancers. Variation of frequency of grade 1 and 2 cancers is represented by the oblique line.

patterns presented above, plus cancer volume. The best predictor of lymph node metastasis was volume of grade 4–5 carcinoma, i.e. the total percentage of grade 4 and 5 multiplied by the total volume of the tumor. Above 3.2 ml of grade 4–5 cancer, 22 out of 38 cases showed nodal metastasis. Only one case of 172 with less than 3.2 ml of grade 4–5 cancer had nodal metastasis. Distribution of cases with positive nodes according to cancer location is shown in Table 1.

Capsular penetration and perineural space invasion

The location and extent of complete capsule penetration by prostate cancer were quantitated in a series of 176 consecutive radical prostatectomy species (5.6).

In 78 of 156 (50%) stage B cancers, and in 4 of 20 (20%) stage A cancers, tumor was seen in the periprostatic tissue after having penetrated through the capsule thickness. Incidence of capsular penetration according to cancer zone of origin was 25% and 51% in transition zone and in non-transition zone cancers respectively. The percentage of complete capsule penetration was increasing in proportion with cancer volume (Table 2), but seen as frequently as 30% in cancers less than 4 ml. Both the occurrence and extent of capsule penetration and the cancer volume were in turn strongly correlated with the presence of lymph node metastasis and with seminal vesicle invasion. However, capsule penetration less than 0.5 cm^2 area appeared to be not significantly different from absence of capsule penetration regarding these two prognostic parameters.

Table 1

Percentage of cases with positive nodes according to cancer location, and volume of grade 4–5 (total cancer volume × % of cancer grade 4 or 5) in a series of 209 radical prostatectomy specimens for prostate cancer

Volume grade 4–5	T.Z. cancers	Non-T.Z. cancers	All cancers
<3.2 ml	0/32 (0%)	1/139 (1%)	1/171 (1%)
>3.2 ml	3/5 (60%)	19/33 (58%)	22/38 (58%)

T.Z. = transition zone

Table 2

Capsule penetration related to cancer volume in stage A versus stage B carcinomas in a series of 156 radical prostatectomy specimens for prostate cancer

Cancer volume	All cases	Cases with capsular penetration
Stage B cancers		
>12 ml	23	20 (87%)
> 4 ml – ⩽12 ml	39	30 (77%)
⩽ 4 ml	94	28 (30%)
All volumes	156	78 (50%)
Stage A cancers		
>12 ml	1	0
> 4 ml – ⩽12 ml	4	2
⩽ 4 ml	15	2
All volumes	20	4 (20%)

The distribution of areas of capsular penetration on the side of the dominant tumor mass was not random over the capsular surface. In non-transition zone tumors, the area of predilection of capsule penetration corresponded to a line running from base to apex posterolaterally and just anterior to the junction of the rectal and lateral surfaces of the prostate. In transition zone tumors, all areas of capsule penetration were anterolateral, near the lateral border of the anterior fibro-muscular stroma. This corresponds to an area where enlarged transition zone by BPH is the closest to the prostatic surface. It represents an area of weakness where the peripheral zone lateral extension ends, and where the anterior fibro-muscular extension narrows.

Among the non-transition zone cancers the dominant mechanism of capsule penetration was found to be progression along perineural spaces, which represent planes of least resistance. The frequency of perineural space invasion, seen in areas of capsular penetration in this group of tumors, was 95% and was found to be the dominant mechanism in 85% of these areas.

The spread of tumor along the perineural spaces explains why capsule penetration areas were not random over the capsule surface. They were concentrated selectively in the areas where nerves from the superior and

inferior pedicle penetrate the prostatic capsule (Fig. 4). Most often, perineural space invasion followed the oblique vertical course of nerve branches that extended superiorly to the superior pedicle near the prostate base. Thirty-nine cases had areas of capsule penetration, where 100% of cancer was within perineural spaces. In 29 of these 39 cases, areas of capsule penetration occupied only less than a third of the total area of contact between the main tumor within the gland and the overlying capsule. In 21 of these 29 cases, capsule penetration areas were limited to an area near or above the superior border of the cancer. Capsular penetration along the nerves of the inferior pedicle was seen in 18 of the 78 cases.

The prostatic capsule which consists of a 1 mm thick layer of transverely arranged smooth muscle bundles and collagen fibers represented a barrier to the growth of prostatic cancer since only 12 of 78 cases (15%) showed a capsular penetration by a predominant mechanism of direct spread of the cancer through the capsule. This mechanism of capsule penetration was not associated with any perineural space invasion in only 4 cases (5%). In each of the 78 cases with an area of capsule penetration, the tumor was molded to the inner surface of the capsule in a large surface.

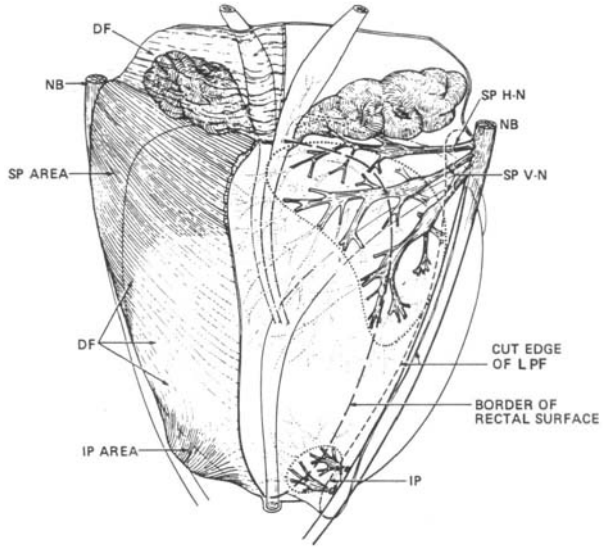

Fig. 4. Distribution of nerve branches to prostate—right posterolateral view. Nerves within neurovascular bundle (NB) branch to supply prostate in a large superior pedicle (SP) at prostate base and a small inferior pedicle (IP) at prostate apex. Branches leave lateral pelvic fascia (LPF) to travel in Denonvilliers' fascia (DF), which has been cut away from right half of prostate. Nerve branches from superior pedicle fan out over a large pedicle area (thickened area of DF). A small horizontal subdivision (H-N) crosses the base to midline; a very large vertical subdivision (V-N) fans out extensively over prostate surface as far distally as midprostate. Branches continue their course within the prostate after penetrating the capsule within a large nerve penetration area (dotted line). The small inferior pedicle has a limited ramification and nerve penetration area (dotted line). (From J Urol 1989; 142: 763).

Seminal vesicle invasion

In a series of 243 radical prostatectomy specimens (3), presence of cancer in the muscular wall of seminal vesicle and/or vas deferens was identified and quantitated. Among these 243 cases, 205 were of non-transition zone origin (201 stage B) and 38 of transition zone origin (24 stage A). Seminal vesicle invasion was identified in 47 (23%) of the 205 non-transition zone cancers. However, none of the 38 transition zone carcinomas showed any evidence of seminal vesicle invasion. The route of invasion from the prostate into the seminal vesicle involved the ejaculatory duct sheath in 43 of 47 cases and in these cases the cancer invaded always at first the proximal area of the seminal vesicles.

The frequency of seminal vesicle invasion increased progressively with volume, and/or with the proximity of the cancer to the mid area of the prostatic base.

The frequency and extent of bilateral involvement increased steadily with volume. The smallest of the 20 cancers showing bilateral invasion was 6 ml as compared to 1 ml for the smallest of the 27 carcinomas with unilateral seminal vesicle invasion.

Relation between seminal vesicle invasion, cancer volume and lymph node metastasis is shown in Table 3.

Seventeen of 20 (85%) cases with positive nodes were among the 47 cases with positive seminal vesicles and, consequently, 17 of 47 (30%) cases with positive seminal vesicles had positive nodes.

Multiple logistic regression analysis was used to test the predictive value of cancer volume and seminal vesicle invasion for nodal metastasis. Each variable alone showed statistically significant predictive value for metastasis ($p < 0.001$). The log of tumor volume was the strongest predictor, and seminal vesicle invasion was the weakest. No increase in predictive value was produced by adding seminal vesicle invasion to tumor volume.

Denonvilliers' fascia invasion

In a series of 243 radical prostatectomy specimens prostate cancer was identified in Denonvilliers' fasica in 45

Table 3

Frequency and extent of seminal vesicle (SV) invasion according to cancer volume in a series of 243 radical prostatectomy specimens extent of SV invaded by cancer is divided into 3 categories (0% less or more than 16%). Lymph node metastases is indicated by the second number in parenthesis

	Extent of SV invasion		
	0	<16%	>16%
>12 ml	4 (1)	12 (4)	10 (7)
> 4 ml – ≤12 ml	37 (2)	12 (4)	6 (0)
< 4 ml	117 (0)	7 (1)	0 (0)

cases. In this study, areas of cancer coursing along perineural spaces at the level of the superior and inferior neuro-vascular prostatic pedicles, which are partly included in Denonvilliers' fascia, were disregarded. In these 45 cases malignant cells were seen progressively between the thick smooth muscular bundles which compose the fascia posterior to the prostate base, around the seminal vesicles, and posterior to the apex.

Cancer in Denonvilliers' fascia represented capsular penetration areas and, in these cases, cancer penetrated first the capsule mainly by perineural space invasion. Then the cancer left these spaces to grow obliquely and vertically along other spaces of least resistance represented by the loose muscular fibers in the Denonvilliers' fascia. Along this route, cancer reached in some cases the posterior aspect of the seminal vesicles from the base, or the thick triangular termination of Denonvilliers' fascia behind the membranous urethra from the apex.

In 41 of 45 cases Denonvilliers' fascia's muscular bundles were invaded behind the prostate base (3 cases), behind the seminal vesicles (21 cases) or both (17 cases). In 10 of 45 cases, the Denonvilliers' fascia's muscular bundles were invaded behind the middle third (2 cases) and behind the apex (8 cases) of the prostate. Among these 45 cases, 76% had a cancer volume above 12 ml, 24% between 4 and 12 ml, and 3% under 4 ml.

Discussion

Our findings on the morphologic and histologic features of transition zone and non-transition zone cancers are of great interest to the urologist since most of stage A cancers are predicted to be of transition zone (BPH) origin and stage B cancers are predicted to be of non-transition zone origin. The anatomic facts concerning site of cancer origin and direction of spread provide a precise definition for stage A cancer which has hereto been lacking.

However, if some features of the natural history differed between transition zone and non-transition zone cancers at early stage, i.e. at the stage of localized cancers, the prognosis of these two cancers as measured by lymph node metastasis was the same in our series. A volume of 3.2 ml of grade 4–5 cancer was the threshold size for appearance of distant metastasis regardless of zone of origin.

Cancers originating in the transition zone remained spherically shaped until sizes of 5 to 10 ml, since they were molded to the boundaries of the enlarged transition zone lobe by BPH i.e. urethra medially, fibromuscular stroma anteriorly, fibrous bands of stroma (plane of enucleation) postero-laterally. These cancers invaded into the periprostatic tissues anterolaterally, and grew within the thickness of the anterior stroma which is in continuity with the bladder neck fibers upwards and the external straited sphincter downwards.

They never invaded into the seminal vesicles. The transition zone appeared to be the site of origin of clear cell carcinomas which represent all grade 1 and 2 cancers and some of grade 3 cancers.

Cancers originating in the non-transition zone showed a spheric pattern of growth until the size of one or two ml; then their growth was stopped by the prostatic capsule and transition zone fibrous boundary. Large cancers had a tendency to fill the peripheral and central zones on both sides. These non-transition zone cancers extended within and outside the prostate along planes of least resistance represented by perineural spaces, ejaculatory ducts sheath and Denonvilliers' fascia. Cancers located at the prostate base, or large cancers grew commonly into the seminal vesicles. Well-differentiated non-transition zone carcinomas represented grade 3 cancers with dark cytoplasm and small glands. Clear cell grade 3 cancers represented less than 3% of all grade 3 non-transition zone cancers.

The cancers developed poorly differentiated areas with time and increasing volumes. These grade 4 to 5 areas of tumor easily transgressed anatomic barriers which were respected by grade 3 carcinomas. Grade 4–5 cancers invaded through the transition zone boundary, left the perineural spaces to spread into the periprostatic tissues, commonly destroying the nerve fibers or ganglion. Metastatic spread was seen only in carcinomas with some grade 4 or 5 areas.

Due to the strong correlation observed between volume of grade 4 or 5 areas and distant metastases, it remains a tenable hypothesis that capsule penetration and seminal vesicle invasion in prostate cancer have no direct biologic significance, and that both are reflections of cancer volume, differentiation and site of origin.

In our series, there were more small stage A cancers than stage B cancers. By definition stage A cancers are incidental carcinomas sampled during a TUR or enucleation. Their volume distribution is similar to the distribution of transition zone cancer from an autopsy series, consisting in the great majority of small well-differentiated cancers. Stage B cancers, which were detected clinically and actually palpated, had a cancer volume superior to 0.2 ml. Since the mean average volume for stage A cancers was smaller than that of the stage B cancers, we would expect stage A cancer discovered at TUR to behave better than stage B cancers. However, the prognosis of the individual cancers was not different in our series between these two groups: distant metastasis occurred at the same volume and differentiation ranges for both stage A and B cancers. Our data do not show whether the doubling time of cancers in these two groups was significantly different or not.

Some practical considerations of this natural history of prostate cancer are of interest for the urologist.

Enucleation of the adenoma, and almost always TUR exclusively sample the BPH areas, i.e. transition zone lobes and peri-urethral glands area (7). A finding of distinctive clear cell areas in TUR samples further substantiates this

site of origin. Our results show that only a minority (14%) of cancers sampled during TUR originated in the non-transition zone. They represent cancers which invaded through the transition zone boundary into the transition zone. The proportion of these cancers in the tissue sample would often be small, and grade 4 and 5 areas should be common.

This situation of small volume of poorly differentiated (grade 4–5) carcinoma, having a bad prognosis due to its belonging to a large peripheral cancer, was included in Jewett's classification A2–A1 (8).

Since transition zone cancers are for a long time confined to their zone of origin, enucleation of adenoma which by definition removes all the transition zone enlarged by BPH, may cure the patient in case of stage A cancer if two conditions are fulfilled: stage A cancer is not present at the margin of the specimen marked with ink, and there is no metastasis at time of surgery. However, in many cases of stage A cancer the TUR does not reach the tumor margin and the total volume, and differentiation cannot be estimated in an adequate way.

Studies of residual BPH on prostatectomy specimens after TUR (7) showed that residual BPH nodules are numerous around the TUR defect, in the anteromedial portion of the gland, and at the apex where they have usually not been resected.

This residual BPH tissue should be sampled first following TUR in stage A cancer in order to know whether the patient still has residual tumor belonging to the same primary tumor found in the TUR chips or not. Distinction should be made between this residual tumor in contact with the TUR defect and a remote secondary incidental cancer not related to the stage A cancer.

If the diagnosis of prostatic adenocarcinoma by rectal palpation depends on the proximity of the cancer to the posterior surface of the gland, less than half (45%) of all carcinomas may be detectable by rectal examination (7). These rectally palpated cancers represent non-transition zone cancers, excluding the small cancers located in the anterolateral areas of these zones, and large transition zone cancers which have invaded into the peripheral zone.

The application of quantitative morphology to the study of prostate cancer biology has made it possible for us to identify the tumor volume of 12 ml as an important landmark in the natural history of tumor progression. Our data on positive surgical margins support this observation, suggesting that cancers above 12 ml are seldom cured by radical prostatectomy alone (9).

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