

HISTOLOGIC CARCINOMA OF THE PROSTATE IN AUTOPSIES: FREQUENCY, ORIGIN, EXTENSION, GRADING AND TERMINOLOGY

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ABSTRACT

Objective: To study the prostate carcinoma incidentally found in autopsies.

Material and Methods: The prostates from 150 autopsied men over 40 years of age were dissected in transitional and peripheral zones. The microscopic examination included presence or absence of adenocarcinoma, neoplastic extension, evaluated by the number of fragments, and histologic grading, according to the Gleason system.

Results: The frequency was 36.66%, being significantly higher in older patients with no predilection to color. From a total of 55 carcinomas, 56.36% were found in both transitional and peripheral zones, 25.45% only in transitional zone and 18.18% only in peripheral zone. All neoplasias found only in the transitional zone or only in the peripheral zone were not extense and had low grade. When found in both zones, the carcinoma was not very extense and had low grade in the transitional zone, but it was extense and with high grade in the peripheral zone. In 14.54%, 80% and 5.45% of the carcinomas, the Gleason score was 2 - 4, 5 - 6 and 7, respectively. Gleason score 2 - 4 was significantly more frequent in younger patients and score 7 in older patients.

Conclusions: There are morphologic evidences of a less malignant potential when the carcinoma is present exclusively in the transitional zone. Final score 2 - 4 was significantly more frequent in younger patients and final score 7 in older patients.

Key words: prostate; prostatic neoplasms; pathology; autopsy; neoplasm staging

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INTRODUCTION

The frequency of incidentally found carcinoma in autopsies of patients with no urological complaints varies from 6.6 to 66.7% (1,2). Most of the times, this wide frequency variation is due to the examination method. Baron & Angrist have shown the wide frequency difference when only routine cuts of the prostate are used and when serial cuts are done. In patients over 50, the frequency was 9.9% when routine cuts were examined and 46% in cases of serial cuts (3).

Most of the carcinomas have their origin in the peripheral zone (PZ) (4,5). It is known that carcinomas which have their origin in the transitional zone (TZ) have better prognosis due to the fact that the morphologic findings and type of growth suggest a less aggressive biological behaviour (6,7).

In a recent editorial, it was recommended not to diagnose adenocarcinoma with a final score 2 - 4 in the Gleason system by prostate needle biopsies (8). One of the reasons was that out of a total of 6032 radical prostatectomies in which the cancer diagnosis was established through needle biopsy,

only in 15 (0.2%) the tumor presented a final score 2 – 4(9).

The carcinoma incidentally found in autopsies, transurethral prostate resections (TPR) and open prostatectomies are similar, including the terms histologic, occult, latent, dormant, and indolent (10,13).

The objective of this study is to study the frequency of the carcinoma incidentally found in autopsies, to look for any morphologic evidence for a possibly better behaviour when the neoplasia has its origin in the transitional zone, to analyze the histologic grading emphasizing the final score 2 – 4 and to discuss the terminology used to refer to this neoplasia.

MATERIALS AND METHODS

The study was performed in 150 consecutive autopsies of men with more than 40 years of age who presented any kind of disease, except for prostate carcinoma. The material was obtained in a 7-year period, from 1974 to 1980. Patients' age and color were obtained from the autopsy report. Regarding color, they were considered white and not white. The last included black and mulattos. A single patient was of Japanese descendance and was not included in the analysis related to color.

The prostates were harvested and immediately fixed in 10% formalin. After a period which varied from 5 days to a month, they were dissected. First, a sagittal cut of the prostate was made, passing through the median line and separating it in two halves. The examination of the cut surface of these two halves reveals the prostatic urethra and the ejaculatory duct. This is presented in the shape of a brown-yellowish line, due to the pigment, similar to the lipofuscin. It extends from the posterior and inferior portions of the prostate to the verumontanum. Then, a cut passing through the plan indicated by the trajectory of the ejaculatory duct was made. The posterior lobe is the portion of the prostatic parenchyma situated posteriorly to this plan, according to Moore (10), Kahler (14) and Strahan (15). It is the largest part of the peripheral

zone and posterior half of the central zone, according to the McNeal classification(16). The part situated before this plan corresponds to the anterior half of the central zone and the whole portion of the transitional zone.

Frontal serial cuts at intervals at 0.3 to 0.5 cm intervals were made in the two parts obtained through the procedure described above. The fragments were processed and included in paraffin, obtaining a cut of each fragment on the side that would guarantee a serial examination. This was possible through a cut on the opposite surface of the fragments cut. Cuts were 6- μ m thick and were stained in hematoxylin-eosin.

In the microscopic examination of the cuts, the following were observed:

a)- Presence or absence of adenocarcinoma. The criteria for this diagnosis were based in the infiltrative characteristic of the neoplastic tissue and in the architectural disarrangement, according to Mostofi & Price (17);

b)- Extension. The tumor volume was indirectly evaluated, analysing the extension of the neoplasia, that is, the number of histologic cuts showing tumor from the total of examined cuts. According to the extension, the neoplasia was considered little, moderate or very extense, respectively, when observed in less than 25%, between 25 and 50% and in more than 50% of the total examined cuts;

c)- Histologic grading. The Gleason's grading system was used (18). Neoplasias with final score 2 – 6 were considered low grade; and, the ones with final score 7 – 10 were considered high grade (19).

The data were statistically analyzed through the chi-square test to determine the differences in proportion at a significance level of 0.05.

RESULTS

Frequency

The frequency of incidentally found carcinomas in autopsies was 55/150 (36.66%). The frequency of the 55 carcinomas according to age is shown on Table-1. The statistic analysis showed a significantly higher frequency with age ($p = 0.015$).

HISTOLOGIC CARCINOMA OF THE PROSTATE IN AUTOPSIES

Table 1 - Frequency of 55 pathologic prostate carcinomas incidentally found in 150 autopsies, according to age.

Age (years)	Carcinoma	%
40 – 49	9/55	16.36
50 – 59	9/55	16.36
60 – 69	17/55	30.90
≥ 70	20/55	36.36

p = 0.015

Table 2 - Extension of 55 incidentally found histologic prostate carcinomas in 150 autopsies, according to the percentage (less than 25%, between 25 and 50%, and more than 50%) of sections showing neoplasia, according to the zone of origin (PZ: peripheral zone, TZ: transitional zone).

Extension	PZ	TZ	PZ + TZ
< 25%	10/10	14/14	17/31 (54.83%)
25 – 50%	0	0	13/31 (41.93%)
> 50%	0	0	1/31 (3.22%)

Origin

The figure shows the frequency of the 55 carcinomas, according to their zone of origin.

Extension

According to the extension, the carcinomas were classified in 3 groups: less than 25%, from 25 to 50%, and more than 50% of the fragments presenting carcinoma. Table-2 shows the extension of 55 carcinomas according to the zone of origin.

In 31 cases, the carcinoma was found in both zones (TZ + PZ). In 16/31 of the prostates (51.61%), its extension was similar in both zones, while in 15/31 (48.38%) the extension was different.

In 19 cases, the extension in the TZ was less than 25%. In 14 of them (73.68%), the extension in the PZ was also less than 25%. However, in 3/19 (15.78%) and in 2/19 (10.52%) the extension was from 25 to 50% and more than 50% in the PZ, respectively.

In 10 cases, the extension was between 25 and 50% in the transitional zone. In 5 (50%) and in 3 of them (30%), the extension was less than 25% and more than 50% in the peripheral zone, respectively. In 2 cases the extension in the transitional zone was more than 50%. In one of them the extension of the peripheral zone was less than 25%, and in the other between 25 and 50%.

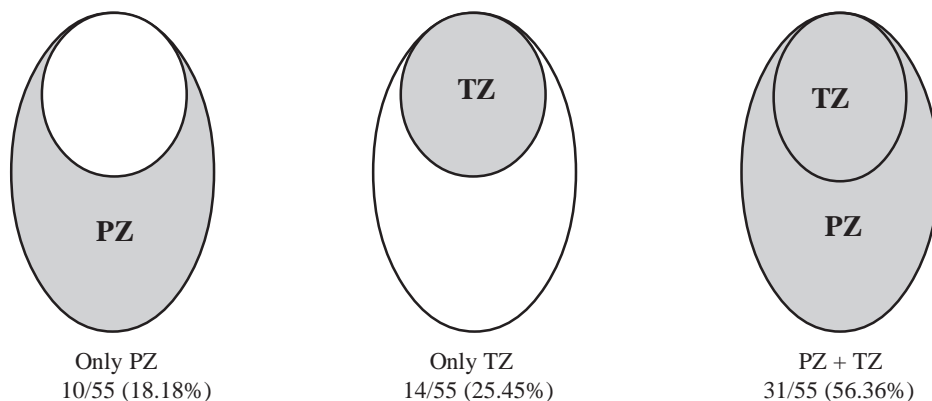


Figure - Frequency of 55 incidentally found histologic prostate carcinomas in 150 autopsies according to the zone of origin (PZ: peripheral zone, TZ: transitional zone).

Table 3 - Gleason’s system score of 55 incidentally found histologic carcinomas in 150 autopsies, according to the zone of origin (PZ: peripheral zone, TZ: transitional zone).

Zone	Low-grade (score: 2 – 6)	High-grade (score: 7 – 10)
PZ	10/10	0
TZ	14/14	0
PZ + TZ	28/31 (90.32%)	3/31 (9.67%)

Histologic Grading

According to Gleason’s grading system, 52/58 (94.54%) of the carcinomas were low grade (score 2 – 6) and 3/55 (5.45%) were high grade (score 7 – 10). From the 52 low grade cases, 8/52 (16.38%) presented score 2 – 4, and 44/52 (85.46%) score 5 – 6. The 3 high grade cases presented score 7.

Table-3 shows the histologic grading (low or high grade) of the 55 carcinomas, according to the zone of origin. All carcinomas found exclusively in the peripheral zone or in the transitional zone were low grade.

Table-4 shows the score of the 55 carcinomas according to age. The statistical analysis showed a prevalence of score 2 - 4 in younger patients and score 7 in older patients (p = 0.011).

Table 4 - Gleason’s system score of 55 incidentally found prostate carcinomas in 150 autopsies according to age.

Gleason Score	Age (Years)			
	40 – 59		≥ 60	
	No.	%	No.	%
2 – 4	6/18	33.33	2/37	5.40
5 – 6	12/18	66.66	32/37	86.48
7	0/18		3/37	8.10

p = 0.011

It’s worth mentioning that from the 31 cases in which the carcinoma was found in both zones (PZ + TZ), the histologic grading was the same in 29 of them. In one case the carcinoma had low grade in the transitional zone, and high grade in the peripheral zone. In another case, the carcinoma had high grade in the transitional zone and low grade in the peripheral zone.

DISCUSSION

Frequency

The frequency of incidentally found carcinomas in autopsies in our study was similar to the observed in the USA, Europe and Asia (3,20-26). The frequency was significantly higher with age (p = 0.015). We did not observe any difference in frequency between white and not white patients (p = 0.775), which seems to indicate that race does not influence the origin of this carcinoma.

Considering that the prevalence of clinical prostate carcinomas is low in Japan, it would be expected that the frequency of incidentally found carcinomas in autopsies was also lower. However, this does not happen. The frequency of this carcinoma in Japan is similar to other countries’ (23-26). It is likely that there is an influence of universally found carcinogen agents in its origin, and that they have their effect potentialized by age. The development of a clinical neoplasia, on the other hand, would be influenced by race and by new carcinogen agents to which the patient is exposed (27,28). This is observed in the Japanese who emigrated to the USA, whose frequency of clinical carcinoma increased (26).

Origin and Extension

Some authors admit the evidence of a different biological behaviour depending on the origin of the prostate carcinoma (6,7,29,30). Greene et al. (29,30) observed that in radical prostatectomies, the carcinomas originated in the transitional zone were well-differentiated, even if large in volume. The ones originated in the peripheral zone were moderately or less differentiated, even if small in volume. These authors have also observed that 93% of the peripheral

zone tumors were associated to high grade prostate intraepithelial neoplasia (PIN), while none of the tumors found in the transitional zone had this association.

Studying radical prostatectomies, Lee et al. (31) observed that 22% of neoplasias originated in the transitional zone presented extraprostatic extension (pT3 stage), while 48% of the tumors originated in the peripheral zone presented this extension. Besides, they observed that the average score according to Gleason's system was 6.2 ± 1.6 and 7.4 ± 0.9 , respectively, to tumors originated in the transitional and peripheral zone.

Grignon & Sakr (6) observed that the proliferation index for tumors originated in the peripheral and transitional zone was 5.0 and 1.6%, respectively. The average score for the 2 groups, according to Gleason's system, was 6.7 and 5.6, respectively.

The morphologic results of this study show that the carcinoma presents a better behaviour only when located exclusively in the transitional zone. In this unique site, all neoplasias had low grade and were less extense. When the carcinoma was located in both zones, it could be low or high grade, and less or more extense. It is worth mentioning that from a total of 31 carcinomas located in both zones, only 14 were less extense in both zones. Three less extense carcinomas located in the TZ were moderately extense in the PZ (25 - 50% of fragments showing neoplasia), and 2 less extense carcinomas in the TZ were very extense in the PZ (more than 50% of fragments showing neoplasia).

Twenty-nine out of 31 carcinomas present in both zones were low grade, according to the Gleason's system. One case, however, was low grade in the TZ and high grade in the PZ.

These findings allow a comment about pT1a stage. Whenever a low grade and less extense (less than 5% of fragments examined) incidental carcinoma is found in prostatic transurethral resection or open prostatectomy, i.e., surgeries which resect the transitional zone, it is likely that the carcinoma is also present in the peripheral zone, more extense and of higher histologic grading. Thus, we believe that a needle prostate biopsy in the PZ would be useful in the evaluation of the therapeutical approach in pT1a stage.

Histologic Grading

In the present study, the frequency of carcinoma with final score 2 – 4 was relatively high, being observed in 8 out of 55 prostates with carcinoma (14.54%). This result contrasts with the 1% frequency in prostate needle biopsies in men who were at the Johns Hopkins Hospital to undergo a radical prostatectomy (8).

Epstein (8) proposes that final score 2 – 4 should not be performed in prostate needle biopsies due to 3 main reasons: in general, this score represents a subgrading of a higher score carcinoma, it does not present a good reproductibility among uropathologists and it can have an adverse impact in the patient's therapeutical behaviour. According to Epstein (8), the first argument is based on the fact that most of the tumors considered score 2 – 4 in prostate needle biopsies show a score 5 – 6 or higher when revised. In a study performed at Johns Hopkins, only 4 carcinomas out of 87 revised prostate needle biopsies continued with a Gleason score 2 – 4 (32). The second reason is a consequence of the low reproductibility level observed in score 2 – 4. In a study performed by 10 uropathologists, there was a consensus in only 1 out of 14 cases considered representative of this score. The third reason, and the most important to Epstein (8), is that considering a carcinoma of such low final score may indicate that the patient does not need a definite therapy .

However, Epstein does not deny the existence of the adenocarcinoma with score 2 – 4 emphasizing that it is observed, more frequently, in TURP (8). Contrary to the material found in TURP, there is another fact that affects the score 2 – 4 evaluation in prostate needle biopsies of the peripheral zone. For a precise diagnosis of this score, it is necessary that the lesion is fully represented, with well-delimited margins and round or oval acines without infiltration or fusion (18,19). It is not possible to be sure if there is a well-delimited margin all over the carcinoma, unless the neoplasia is smaller than 1mm of diameter. Consequently, even if the adenocarcinoma is really low grade in a prostate needle biopsy, the diagnosis of score 2 – 4 will always be in probability, because of the sample size (34).

The higher frequency of adenocarcinoma with score 2 – 4 in autopsies when compared to the frequency in prostate needle biopsies is due to 2 facts. Part of these neoplasias may not increase the PSA and, consequently, there is no indication for a biopsy, since the origin is in the peripheral zone. This is due to the fact that low-grade neoplasias originated in the transitional zone can present higher serial levels of PSA when compared to neoplasias originated in the peripheral zone (35,36). The second fact, and maybe the most important one, are the microscopic difficulties previously described in the scoring of needle biopsies.

There was no difference related to color ($p = 0.217$), but the adenocarcinoma with Gleason score 2 – 4 was significantly more frequent in younger patients and score 7 in older patients ($p = 0.011$).

This distribution according to age may help to answer an unsolved question: do clinical prostate carcinomas start as well-differentiated tumors (low grade) and gradually become less differentiated (high grade), or do these neoplasias have fixed histologic grades, that is, do they start low grade or high grade without any substantial changes in grading? (37). Our results support the first hypothesis, showing a higher frequency of carcinomas with score 2 – 4 for patients aged 40 – 59, and score 7 for patients ≥ 70 years old.

Terminology

Moore (10) and Rich (11) were the first authors to name the carcinoma incidentally found in autopsies as “occult carcinoma”. The term is not appropriate, once it is usually used to refer to carcinomas which appear by metastasis and not by symptoms or signs resulting from their places of origin (38).

The term “latent” was initially used by Andrews (12), but also in an inappropriate way. This and other terms such as “dorment” (13) and “indolent” (39) refer to the biological behaviour of the tumors. The idea of a “latent”, “dorment” or “indolent” behaviour of the prostate carcinoma is based on epidemiologic features (40,41), as it is likely that this carcinoma may develop or not in a slower way when compared to the clinical carcinoma. If we

compare the frequency of incidentally found carcinoma in autopsies to the prevalence and mortality rate of the clinical carcinoma, we can notice a discrepancy. A 50-year-old man with a life expectancy of more than 25 years has a 42% risk of having an incidentally found carcinoma, while the risk of developing a clinical cancer is around 10%, and the risk of death due to this cancer is 3% (40,41).

Thus, it is necessary to refer to carcinoma incidentally found in autopsies, TURP or open prostatectomy in a way that does not implicate the biological behaviour. The carcinoma found like that is purely morphologic and the best terminology is histologic carcinoma incidentally found in autopsies, TURP or open prostatectomy (13).

Unfortunately, we still do not have individual markers to identify the carcinomas which will remain latent or indolent, or those which will develop to clinical forms, invading close organs and eventually killing the patient due to metastasis. Nowadays, the criteria used to make this differentiation is based on probabilities. Thus, for example, in cases of TURP, in which a histologic incidentally found carcinoma is low grade and occupies less than 5% of the resected fragments, corresponds to a pT1 stage and means that it will probably behave as a latent carcinoma. However, this study has shown that, in some of these cases, in the peripheral zone, the carcinoma can be high grade and extense, and therefore more likely to behave as a clinical or aggressive cancer.

CONCLUSIONS

The frequency of histologic incidentally found carcinoma in autopsies is similar to the observed in other countries, being significantly higher in older patients with no predilection to color.

There are morphological evidences of a less aggressive behaviour only when the carcinoma is located exclusively in the transitional zone: all neoplasias originated only in this zone were not very extense and had low grade. It was observed that in some cases of carcinomas located in both zones (TZ + PZ), the extension and the histologic grading could vary according to the zone analyzed. Therefore, in cases of a pT1a stage in which the carcinoma is low

grade and occupies less than 5% of the fragments examined, it can have high grade and be extense in the peripheral zone. It seems that, in this stage, a biopsy of the peripheral zone is useful to evaluate the therapeutic approach.

The frequency of carcinomas with final score 2 – 4 in autopsies is slightly higher than the frequency observed in needle biopsies. This difference is probably due to microscopic difficulties in stablishing this final score in needle biopsies. The final score 2 – 4 was significantly more frequent in younger patients, and score 7 in older patients. This seems to support the hypothesis that clinical prostate carcinomas start as well-differentiated tumors and gradually become moderate and high grade carcinomas.

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EDITORIAL COMMENT

Prostate carcinoma is the most frequent tumor in Brazilian men, according to recent numbers from the National Cancer Institute. It is believed that 21,000 new cases of prostate cancer have been diagnosed in 2001. It was the cause of more than 7,000 deaths, representing a 44% increase when compared to the numbers in 1999 shown by the same institute. The increase in the diagnosis of prostate carcinoma may be due to the increase in its detection, which was made possible by the PSA measurement. However, the number of prostate cancer in Brazil is probably underestimated when compared to the statistics published in the USA.

The present study gives important information for a reflection about the prostate cancer in our country.

The male population in Brazil is composed by 83,576,016 men. According to the Census 2000 from the Brazilian Institute of Geography and Statistics, 5% of these men (4,380,575) are over 65 years, twice as many people at this age in 1991. As proposed in this article, the incidence of prostate cancer is of 37% of these men. In other words, 1,620,812 men would have cancer, 10% of whom would present clinical symptoms and 48,624 would die of the disease. As we can notice, the official numbers are very different from the statistics. As discussed in this article, this discrepancy is not unexpected because the numbers of incidental prostate cancer are similar in many countries. However, its progression is rather irregular and depends on genetic, racial and environmental factors.

The racial genetic factors are the most interesting ones and are predominantly related to the polymorphism of the gene which codifies the androgen receptor located in the X chromosome. The Asians have a long repetitive region while the Black have a very short one and the Caucasians an intermediate one. The longer this polymorphic repetition, the less the sensibility of the receptor (1,2). In Brazil, we have a population of mixed races, whose genetic inheritance is hard to determine, due to lots of migrations and inter-racial marriages. A study about this polymorphism in our population would be revealing.

Another well-known factor subject of many publications is the eating habits. There is a direct relation between the intake of animal fat, specially red meat and dairy products, and the development of prostate cancer (3). Similarly, it seems that the intake of omega-3 fatty acid found in cold-water fish (4), of substances like lycopene(5), found in tomatoes, and of vitamin-E and selenium(6) can protect men against the development of prostate tumors. The Brazilian diet is based on grains and vegetables, which can be a factor of protection against the progression of prostate cancer.

Despite these peculiarities, we must be concerned about the lack of detection of prostate carcinomas in our country. The published study has shown a considerable number of significant tumors, as more than 45% of the tumors occupied more than 25% of the gland, 10% presented high Gleason's score, and 74% presented some kind of peripheral zone compromising.

Since Stamey et al. publication (7), it is believed that the site of lesion is the most important prognostic factor in prostate carcinomas. It is also believed that tumors located exclusively in the transitional zone are indolent, well-differentiated and maybe do not need intervention. All the others are potentially aggressive and men with life expectancy of more than 10 years will suffer from the progression of the disease (8,9).

Some practical issues are also in this article. In spite of the benign development of carcinomas located in the transitional zone, this tumors have been associated with a peripheral zone lesion in 56% of the cases. Thus, as emphasized in this article, if an adenocarcinoma is found in a transurethral, retropubic or transvesical resection of the prostate, a transretal biopsy of the peripheral zone guided by ultrasound should be performed, as this zone is inaccessible through the mentioned surgical procedures.

Another interesting fact in this study is the evidence that the prostate adenocarcinoma has a progression, and that it can progress from a well-differentiated carcinoma to a high-grade tumor, with a higher number of high grade carcinomas, according

to Gleason's score, among older patients. These data suggest that tumors initially detected as well-differentiated in a patient with long life expectancy should be treated as soon as the diagnosis is made, or at least followed for a prompt intervention in case of a transformation.

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