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Original Articles

Early (Stage A) Prostatic Cancer

IV. Methodological Criteria for Histopathological Diagnosis*

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Summary. This study was performed in order to elucidate some of the problems of incidence, morphology and natural history concerned with Stage A prostatic cancer or prostatic microcarcinoma (PMC).

The prostates of 100 patients, treated by subtotal prostatectomy for benign prostatic hyperplasia (BPH), were studied by comparing both routine and step-section techniques. The incidence of PMC was 41% by the former and 86% by the latter technique. Assessment of the size of PMC, as measured by the sum of the two main diameters, resulted in three groups: A_1, A_2, A_3. The last of these may represent a frankly malignant condition, judged by size and the histological appearance. Radical prostatectomy is strongly suggested as appropriate therapy for this group.

Key words: Prostatic cancer – Stage A carcinoma – Prostatic microcarcinoma – Early, latent, unsuspected, incidental carcinomas – Benign prostatic hyperplasia.

Introduction

Stage A prostatic carcinoma (see Whitmore et al., 1973; Prout, 1977) occurs in patients without clinical manifestations of prostatic carcinoma. Several other terms are in use to describe this condition (latent, unsuspected, etc.); for various reasons they appear less appropriate (Battaglia et al., 1974 and 1978) than prostatic microcarcinoma (PMC). This term, which corresponds to the Stage A prostatic carcinoma, stresses its main characteristic: the small size. There are wide variations in the incidence of PMC, as judged by reports of (i) autopsy series (from 1.82% of Berg et al., 1971, to 9.9% of Rich, 1935, 20.5% of

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Table 1. Recorded incidence of PMC (combined histological and clinical series) for BPH-prostatectomized patients

Authors and year	Number of prostatectomies for BPH	PMC	
		No. of cases	%
Kimbrough and Rowe (1951)	435	4	0.9[b]
Higbee (1953)	572	10	1.7[b]
Young (1933)	3907	76	1.94[b]
Turner and Belt (1957)	1665	52	3.12[b]
Bergman et al. (1955)	874	31	3.5[b]
Szendroi et al. (1972)	1816	67	3.69[b]
Bibus (1937)	430	20	4.6[a]
Allemann (1952)	280	14	5.0
Denton et al. (1965)	500	30	6.0
Bauer et al. (1960)	839	55	6.5[b]
Melchior et al. (1974)	644	44	6.8[b]
Battaglia et al. (1978)	1038	76	7.32[b]
Joslin (1961)	748	58	7.7
Wade (1914)	130	10	7.7
Mathe' and Ardila (1947)	337	28	8.3
Edwards (1955)	23	2	8.69
Ekman (1959)	407	37	9.09
Labess (1952)	98	9	9.2[a]
Franks (1954)	200	19	9.5[a]
Smith and Woodruff (1950)	62	6	10.0
Lilien et al. (1968)	115	12	10.4[b]
Thomson Walker (1922)	95	11	11.57
Ferguson (1933)	1426	183	12.8
Miller and Seljelid (1971)	566	73	12.8
Treiger et al. (1948)	108	14	12.96
Albarran Halle' (1900)	100	14	14.0
Jordan and Kraeger (1967)	100	14	14.0
McCrea and Karafin (1955)	2323	328	14.11
Finkle (1954)	141	20	14.18
Swan (1923)	28	4	14.28
Kimbrough (1956)	965	164	16.9
Denton et al. (1965)	100	21	21.0[a]
Myers (1937)	75	22	29.4[a]
Present series	100	86	86.0[a]

[a] Figures refer to step-section technique

[b] Figures refer to data corrected by the Authors of this paper: over-sized cancers have been discarded

Moore, 1935, 30% of Butler et al., 1959, 48.5% of Hirst and Bergman, 1954); and (ii) combined histologic and clinical series (see Table 1).

The conflicting figures probably result from multiple factors, chiefly the age of the patients and the number of specimens examined. Routine and step-section techniques were compared on autopsy-material by Baron and Angrist (1941), Edwards et al. (1953), Scott et al. (1969) and Yatani et al. (1974): the figures for positive findings increased from 9.9% to 46.3%, from 15.18% to 20.23%, from 22.5% to 42.4% and from 7.5% to 27.29%, respectively. In surgi-

cally removed material, a sharp increase (from 6.0% to 21.0%) was observed by Denton et al. (1965).

The present report attempts to compare the results of these two methods on surgically removed material and to deal with some related problems of incidence, morphology and natural history.

Materials and Methods

The prostates of 100 patients treated by subtotal prostatectomy for benign prostatic hyperplasia (BPH) were studied. The entire material received was cut (cross sections of 4–5 mm thickness) and embedded. The resulting blocks examined ranged from 2 to 3 in number for the routine technique and from 4 to 63 for the step-section technique. 2355 supplementary blocks were examined, the average number of blocks for each prostate being 23.55. 2 to 4 sections were cut from each block. All sections were stained with haematoxylin-eosin. Selected sections were stained with PAS-haematoxylin and van Gieson. When PMC was not detected in the first slides (17 cases), further 60 slides for each case were examined.

Results

Table 2 shows both the data obtained by routine and step-section techniques. PMC incidence increased from 41 to 86% using the more intensive method. Three cases of PMC were detected by further sections.

The ratio of positive blocks/negative blocks ranged from 2.38 to 85.00 in different cases, the average number of blocks with detected PMC was 26.04. The sum of the data listed in the table reveals that the number of false-negative diagnoses was 45. The incidence of false-negative diagnoses is influenced by the number of blocks, as shown by Table 3. False-negative diagnoses were not observed in the present series if approximately 50 blocks were taken. Size, multiplicity

Table 2. Incidence of PMC as shown by routine and step-section techniques. Results are separated according to the suggested substaging score

Age at prostatectomy	No. of cases	Routine technique			Step-section technique		
		A_1	A_2	A_3	A_1	A_2	A_3
51–55	4	1	1	0	1	2	0
56–60	10	4	0	1	8	0	1
61–65	19	7	1	0	11	4	0
66–70	36	11	0	1	18	10	3
71–75	20	1	4	5	4	8	7
76–80	10	1	1	1	3	4	1
>80	1	1	0	0	0	1	0
Total	100	26	7	8	45	29	12
			41			86	

Table 3. BPH and PMC: distribution of the false-negative diagnoses (45 cases) in connection with supplementary performed blocks

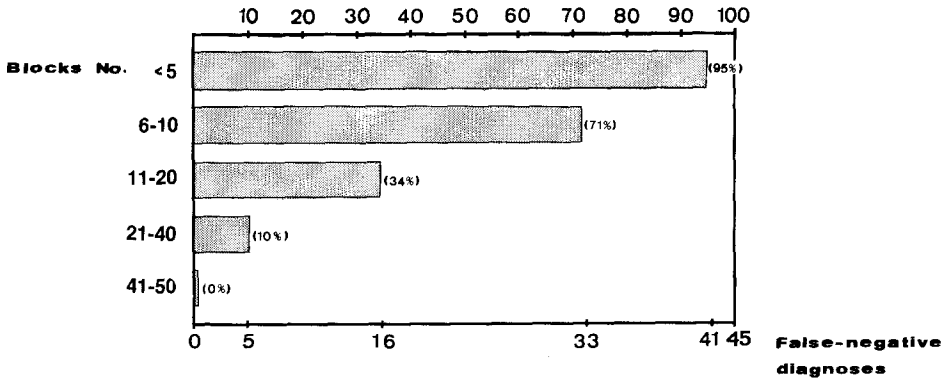


Table 4. Suggested PMC-substaging score: A_1, A_2 and A_3 in order according to size, multiplicity and variability of histological pattern

Substage	No. of cases	$d+d_1$[a]	Bicentric (%)	Multicentric (%)	Multiple histologic pattern (%)
A_1	45	$\leqq 2$	80	20	0
A_2	29	>3 $\leqq 9$	58.62	41.38	0
A_3	12	>10 $\leqq 20$	25.00	75.00	41.66
All substages	86	from $\leqq 2$ up to $\leqq 20$	65.11	34.89	5.81

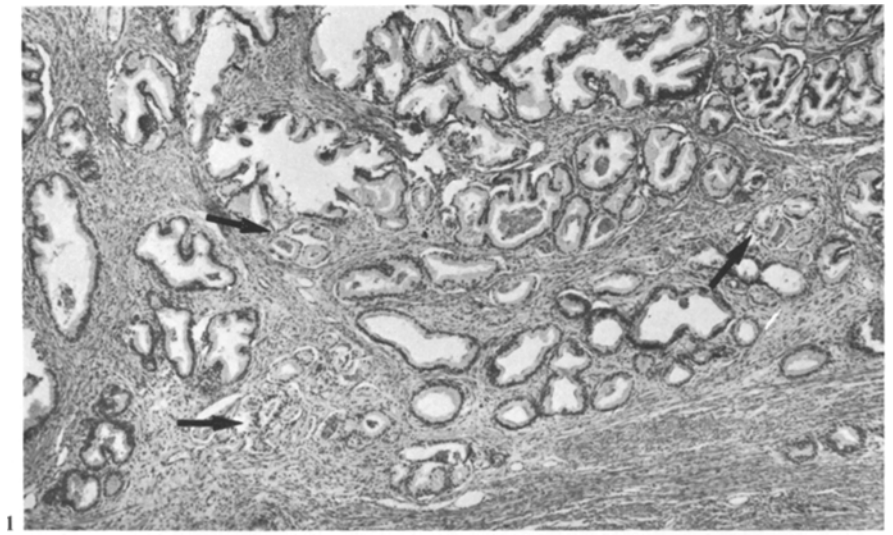
[a] Results given for size are the sum of the two main diameters measured in millimeters

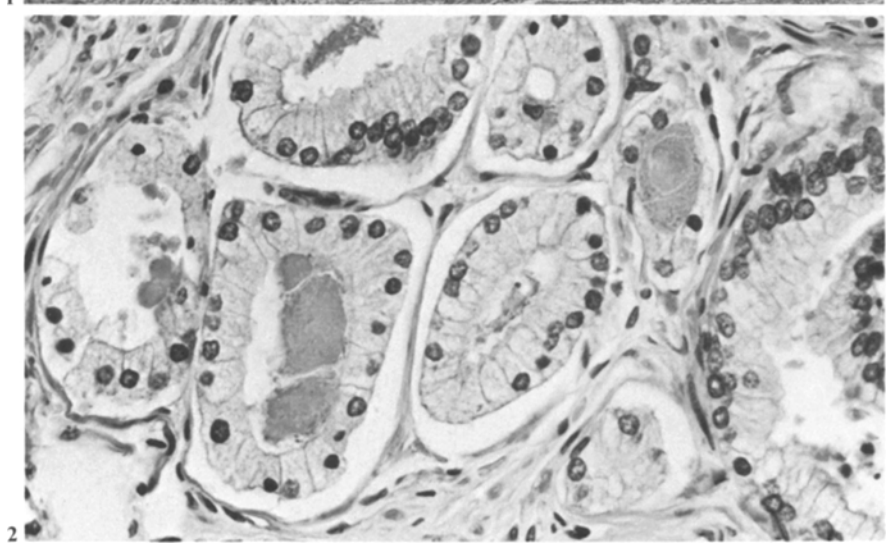
and histologic pattern are correlated in Table 4. PMC is measured by the sum of the two main diameters and graduated in subgroups: A_1, A_2, and A_3. The difference in size is shown in Figs. 1, 3 and 4.

Bicentric or multicentric foci were the rule, no single focus was found. The number of multicentric foci increased from A_1 to A_3. Histologically A_1 and A_2 substages were clear-celled tubular adenocarcinomas while A_3 showed variable histological patterns (7 clear-celled tubular adenocarcinomas, 4 cribriform adenocarcinomas and 1 dark-celled tubular adenocarcinoma). The decrease of A_1 and the corresponding increase of both A_2 and A_3 in connection with age are shown in Fig. 5.

Discussion

From Table 5 it is evident that PMC accounts for a low percentage of all prostatic carcinomas (Stage A, B, C, D), but this finding must be treated with caution since staging systems are far from standardized.





Figs. 1–4. PMC-substaging score (A_1, A_2, A_3)

Fig. 1. Substage A_1. Clear-celled tubular adenocarcinoma. Three small foci are noticeable (↗). (Haematoxylin-Eosin, ×32)

Fig. 2. Detail of Fig. 1. Note the absence of basal cells in the neoplastic tubules. (×320)

The main systems in use in these studies were: A, B, C, D (Whitmore, 1956, 1973); I, II, III, IV (Vacurg) and TNM (UICC), these were compared by Flocks (1973), Barnes et al. (1976) and Prout (1977).

Newer and/or personal stages and substages were subsequently used: A_1, A_2, B_1, B_2, etc. (Hudson and Howland, 1972; Jewett, 1975; McLaughlin et al.,

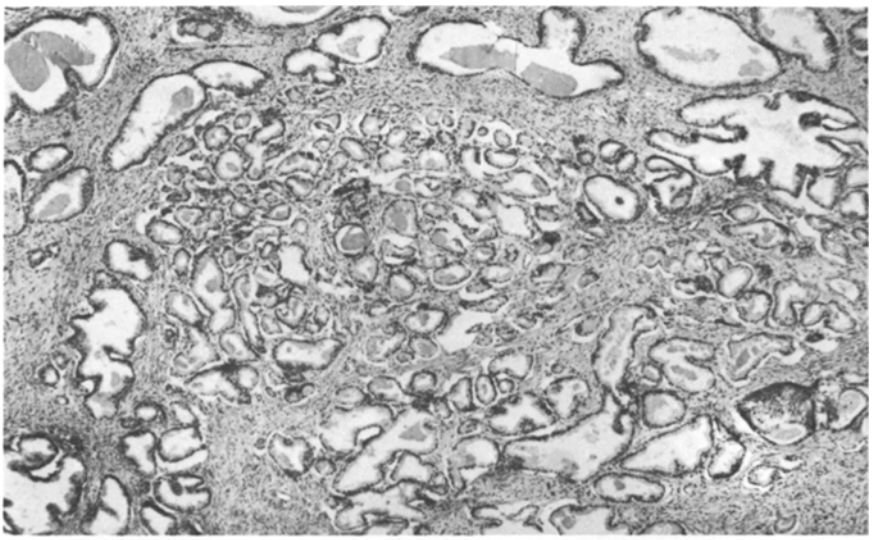


Fig. 3. Substage A_2. Clear-celled tubular adenocarcinoma. (Haematoxylin-Eosin, ×32)

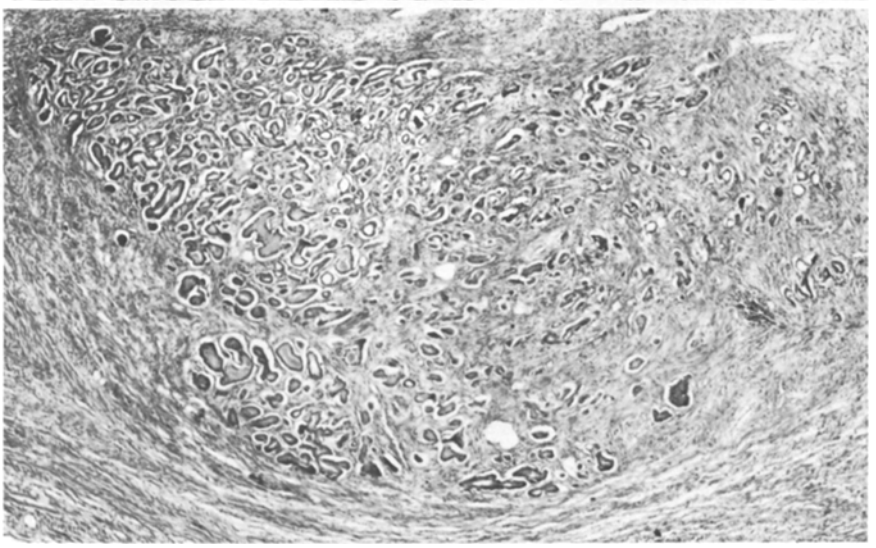


Fig. 4. Substage A_3. Dark-celled tubular adenocarcinoma. (Haematoxylin-Eosin, ×32)

1976; Ray et al., 1976; Bagshaw et al., 1977; Bruce et al., 1977; Wilson et al., 1977; Golimbu et al., 1978). Corriere et al. (1970) used a personal A, B, C, D system which does not correspond with the original A, B, C, D, Whitmore scheme exactly. Other schemes were also used: 0, I, II, III (Flocks, 1969); 0, A, B, C, D (Dhom, 1974, 1977, 1978; Dhom and Hautumm, 1975) and Flocks (1963) and Culp (1967) mistook grading for staging-score.

Because of difficulties of this type some series are not listed in Table 5. Several attempts have been made to correlate grading to staging-score (Andersen,

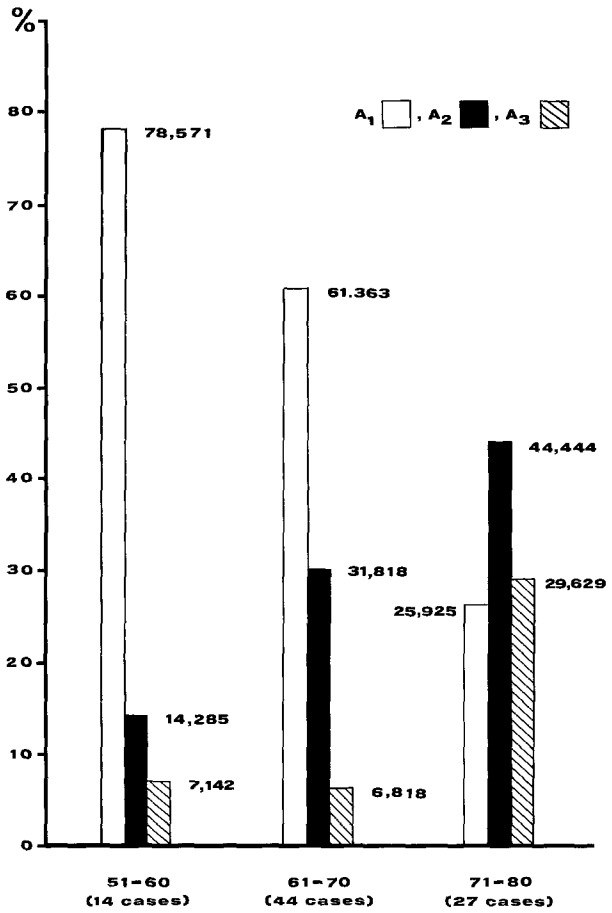


Fig. 5. Incidence of A_1, A_2 and A_3 per age-group. (The only case over 80, not reported in the Figure, was A_2-PMC)

1969; Culp, 1967; Byar et al., 1972; Byar and Mostofi, 1972; Barnes et al., 1976; Gleason et al., 1977).

Owing to the lack of suitable standardized criteria the results were poor despite the apparent clinical value.

In our opinion staging-score should refer chiefly to tumour-size and not to rectal palpation. According to Eberhart and Morgan (1959) the value of the latter has been overestimated (50% of false-negative diagnoses) and it does not seem as reliable as Kimbrough (1956) suggested. Furthermore, when not supported by a standardized histological classification, grading-score, too, is difficult to evaluate.

The step-section technique revealed a PMC-incidence of 86% in our series. Compared with our findings, figures in the literature (Baron and Angrist, 1941; Edwards et al., 1953; Denton et al., 1965; Scott et al., 1969; Yatani et al., 1974) are rather low, usually due to PMC being mistaken for atypical hyperplasia

Table 5. Distribution of the various stages of prostatic carcinoma

Authors and year	Stage A		Stage B		Stage C		Stage D		Total Number of cases
	Number of cases	%	Number of cases	%	Number of cases	%	Number of cases	%	
Andersen (1959)	56	17.8	104	33.0	122	38.0	33	10.0	315
Flocks (1963)	2	4.0	15	30.0	29	58.0	4	8.0	50
Culp (1967)	31	25.0	82	67.0	9	7.0	1	1.0	123
Mellinger et al. (1967)	22	8.14	9	3.33	142	52.50	97	35.92	270
Vacurg (1967a)	118	5.75	170	8.28	992	48.34	772	37.62	2052
Vacurg (1967b)	120	5.18	179	7.72	1110	47.92	907	39.16	2316
Murphy et al. (1969)	18	9.72	47	25.40	39	21.08	81	43.78	185
Byar and Mostofi (1972)	52	25.0	113	54.32	36	17.30	7	3.36	208
Carlton et al. (1972)	6	3.0	73	32.0	61	27.0	85	38.0	225
Schoonees et al. (1972)	32	9.30	37	10.75	117	34.01	158	45.93	344
Gleason et al. (1974)	66	6.39	83	8.84	504	48.83	379	36.72	1032
Murphy et al. (1975)	49	6.36	122	15.84	270	35.06	329	42.72	770
Varkarakis et al. (1975)	2	2.4	20	23.8	24	28.6	38	45.2	84
Varkarakis et al. (1975)	4	4.7	7	8.2	72	84.7	2	2.4	85
Byar and Vacurg (1977)	193	4.99	245	6.34	1877	48.60	1547	40.05	3862
De Vere White et al. (1977)	31	15.04	34	16.50	73	35.43	68	33.00	206
Gleason and Vacurg (1977)	296	10.16	243	8.34	1328	45.62	1044	35.85	2911
Tomlinson et al. (1977)	42	21.0	24	12.0	52	26.0	82	41.0	200
Total	1140	7.49	1607	10.54	6857	44.99	5549	36.41	15238

(Battaglia et al., 1974, 1978). For instance (see Table 1), we defined as PMC some cases diagnosed by the authors (Miller and Seljelid, 1971) as marked or slight atypia. Similarly a diagnosis of atypical glandular proliferation and/or atypical glandular hyperplasia (Liavåg et al., 1972; Harbitz and Haugen, 1972; Akazaki and Stemmermann, 1973) sounds rather suspicious, particularly when referred to "an atypical pattern without clear evidence of invasive growth."

The size of PMC, as measured by the sum of the two main diameters, ranged from less than 2 mm to 20 mm in our series (Table 4). Single diameters ranging from 4 mm to 10 mm and more (Scott et al., 1969), 10 to 15 mm (Edwards et al., 1953), less than 5 to more than 15 mm (Akazaki and Stemmermann, 1973), 2 mm to 20 mm (Andrews, 1949), 5 mm to 20–30 mm (Hirst and Bergman, 1954), 0.3–1 mm to 25–30 mm (Yatani et al., 1974) and (Franks, 1954) from 1 up to 40–50 mm(!) have been recorded by other authors. The higher values make us suspect that, at least in some cases, the carcinomas were too large to be classified as Stage A. The percentage of bicentric and multicentric foci

Table 6. Follow-up survey of patients previously treated by subtotal prostatectomy for BPH: clinically observed prostatic carcinomas

Authors and year	No. of prostatectomized-patients	Prostatic carcinoma	
		No. of cases	%
Holgrewe and Valk (1964)	748	6	0.8
Johnson (1962)	925	14	1.5
McDonald and Coburn (1954)	617	10	1.6
Caine (1954)	519	15	2.9
Ekman (1959)	272	19	6.9
Bakalim (1952)	258	16	8.7

which was 100 in our series is definitely lower in the literature, ranging from 6.75% of Scott et al. (1969), 10% of Yatani et al. (1974), 24% of Blennerhassett and Vickery (1966), 25.0% of Munsie and Foster (1968), 27.58% of Edwards et al. (1953), 33.33% of Franks (1954), 34.04% of Oota (1961), 36.61% of Butler et al. (1959) and to 38.70% of Akazaki and Stemmermann (1973). A few papers quoted higher figures (60% Kastendieck et al., 1976 and 85% Byar and Mostofi, 1972), but these papers were mainly concerned with more advanced stages.

The relationship of BPH to prostatic carcinoma is much debated. Some authors (Moore, 1935; Gaynor, 1938; Kahler, 1939; Baron and Angrist, 1941; Meyenburg and Cathomas, 1948; Dontenwill and Wulf, 1958; Dhom, 1974; Greenwald et al., 1974; Yatani et al., 1974; Dhom and Hautumm, 1975; Barnes et al., 1976; Rotkin, 1977) consider it to be coincidental when the two diseases co-exist, others (Dossot, 1930; Andrews, 1949; Edwards et al., 1953; Harbitz and Haugen, 1972; Szendroi et al., 1972; Mostofi and Price, 1973; Armenian et al., 1974; Kastendieck et al., 1976) suggest a relationship. Armenian et al. (1974) underline that the figures quoted by Greenwald et al. (1974) resulted from an inadequate sample; the follow-up of prostatectomized patients is not comparable with the follow-up of patients without prostatic disorders. Observed figures may show findings which relate to the prostatectomy, which removes neoplastic centres as well as the benign hyperplastic nodules. Latent carcinoma was found to be 2.7 times more frequent in prostates of patients with BPH (Andrews, 1949, Edwards, 1953). Armenian et al. (1974) state that when compared with non-prostatic patients BPH-patients have a 3.7 times higher oncogenic risk. According to Kastendieck et al. (1976) and Kastendieck (1977) the possible relationship of BPH with prostatic carcinoma may be modulated by a dysplastic intermediate stage.

What biological and prognostic meaning can be attributed to PMC? Tables 6 and 7 are concerned with the follow-up of patients treated by prostatectomy for BPH and unsuspected carcinoma respectively.

As shown by the Tables, unsupected carcinomas are a serious neoplastic problem and therefore we agree with Munsie and Foster (1968), that they are not "a histologic curiosity without clinical significance." In our opinion, the follow-up usually available in the literature may well result from questionable criteria

Table 7. Progression of unsuspected carcinomas in BPH prostatectomized-patients

Authors and year	No. of cases		
	Original series	With progression	%
Nesbit and Baum (1951)	42	2	4.76
Corriere et al. (1970)	18	1	5.55
Belt and Schroeder (1972)	185	13	7.02
Lehman et al. (1968)	25	2	8.0
Munsie and Foster (1968)	19	2	10.52
Greene and Simon (1955)	82	12	14.63
Correa et al. (1974)	45	8	17.77
Turner and Belt (1957)	76	14	18.42
Barnes et al. (1976)	70	13	18.57
Blackard et al. (1971)	91	17	18.68
Jewett et al. (1968)	86	21	24.41
Barnes and Ninan (1972)	108	28	25.92
Cook and Watson (1968)	19	5	26.03
Culp and Meyer (1973)	115	34	29.56
Bauer et al. (1960)	40	16	33.33
Miller and Seljelid (1971)	27	9	33.33

or insufficent data. Quite often the follow-up is restricted to traced cases of diagnosed PMC: when series with a low PMC percentage are reviewed, false-negative diagnoses may have been made. Survival data are also generally presented in a crude form and it is then difficult to ascertain the exact health of the patients (clinically healthy and not tumor-bearing or clinically healthy and tumor-bearing). Autopsy data are mainly concerned with the cause of death. It may be possible to present a too optimistic clinical future: it should be borne in mind that "many patients die with their cancers rather than because of them" (Lehman et al., 1968).

In our opinion prostatic carcinoma following subtotal prostatectomy may result from residual substage A_3-PMC.

The last problem to be considered is the management of PMC. From our experience, wait and periodical clinical control for both A_1 and A_2 and total prostatectomy – in suitable cases – for A_3 is the best choice. This choice might settle the old question between urologists who do (Hinman and Hinman, 1949; Smith and Woodruff, 1950; Goodwin, 1952; Hudson et al., 1954; Emmett and Barber, 1962; Jewett, 1970; Kopecky, 1970; Hudson and Howland, 1972; Culp and Meyer, 1973; Nichols et al., 1977) or do not (Nesbit and Baum, 1951; Edwards, 1955; Pool and Thompson, 1956; Colston, 1959; Bauer et al., 1960; Montgomery et al., 1961; Wiederanders et al., 1963; Barnes, 1964; Denton et al., 1965; Cook and Watson, 1968; Corriere et al., 1970; Byar et al., 1972) support radical treatment.

A clear choice is allowed by combining a careful clinical search with the step-section technique. The limiting factor is the large technical effort required

by the technique which – when referred to usual biopsy-schedule (Hinman and Hinman, 1949; Denton, 1967; Leffer and Rosier, 1977; Linoli, 1977) – poses financial and staffing problems.

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