

CARCINOMA OF THE BLADDER: CHARACTERISTIC MODES OF LOCAL INVASION

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It is now fairly generally agreed that the type of treatment to be chosen for an infiltrating carcinoma of the bladder will depend at least to some extent upon the depth to which this tumor has invaded the wall of the bladder. However, the preoperative estimate of this depth of infiltration cannot be expected to equal in precision the postoperative or postmortem findings based upon the study of the whole thickness of the bladder wall. But any information that might increase the accuracy of one's preoperative estimate should be fully utilized. Preoperative segregation, by biopsy of the bladder wall and bimanual palpation of the bladder, is usually simple in most cases of small superficial tumors and large deep tumors. There are two situations, however, in which misinterpretation of the preliminary findings results in the preoperative classification of the tumor as superficial when in reality it is very deep. These two sources of error are attributable to the manner in which certain tumors invade the wall of the bladder, and the first is illustrated by the following case.

A 56-year-old man (B.U.I. 55800) was referred on December 3, 1956 because of intractable vesical irritability 14 months in duration. In the beginning the urine was sterile and biopsies had shown only chronic inflammation. On admission the only positive findings were pyuria with drug-resistant bacilli, a small bladder capacity, and bullous edema of the trigone and bladder neck. Biopsies again revealed only chronic cystitis. After 7 months of regular treatment with instillations and irrigations scattered areas of splotchy reddening were visible and biopsy of these showed marked epithelial pleomorphism suggestive of noninvasive carcinoma. On October 24, 1957 a number of small papillary tumors were present and these on biopsy were found to consist of poorly differentiated squamous carcinoma invading only the superficial muscle and several nearby lymphatics. The outlook was considered favorable because of only superficial infiltration

as disclosed by transurethral biopsies, and on November 11, 1957, the urine was diverted by an ileal loop, and the bladder removed. Retroperitoneal metastases were present. Sections through the bladder wall showed poorly differentiated squamous carcinoma invading as a mass only as far as the superficial portion of the musculature but metastasizing through the lymphatics to the perivesical fat and prostate (figs. 1 and 2). Following discharge from the hospital the patient's course was steadily downhill and he died on January 14, 1958. At post-mortem examination widespread metastases were found in nodes, liver, and bone-marrow.

The first error was the apparently unavoidable delay in finding this elusive tumor; the error in judging it to be superficial, and therefore localized to the bladder, lay in the failure to recognize the significance of local lymphatic involvement as shown by biopsy. Whenever such involvement can be demonstrated, the likelihood of intramural metastasis is always considerable.

To see how often tumors metastasized through the bladder wall in this manner, microscopic slides of 303 cases of infiltrating carcinoma of the bladder were critically studied. These sections had been taken from specimens obtained by autopsy, cystectomy, and segmental resection. The cases were separated into the following 4 stages of infiltration: A, submucosa only; B₁, less than halfway through the muscle; B₂, halfway or more through the muscle; C, perivesical fat or prostate. Fifty-one cases had to be eliminated from the 206 in stage C because of insufficient data, leaving 155 in this group. The total series therefore consisted of 252 cases (table 1).

Although the lymphatics were found to be invaded at some level in the bladder wall in 79 cases (31 per cent), they were involved in only seven in which the tumor had failed to extend to the halfway level in the muscle wall. Of these seven, only two, both poorly differentiated squamous cancers, metastasized to a depth greater than that reached by the primary growth. The results of a detailed analysis of the relation-

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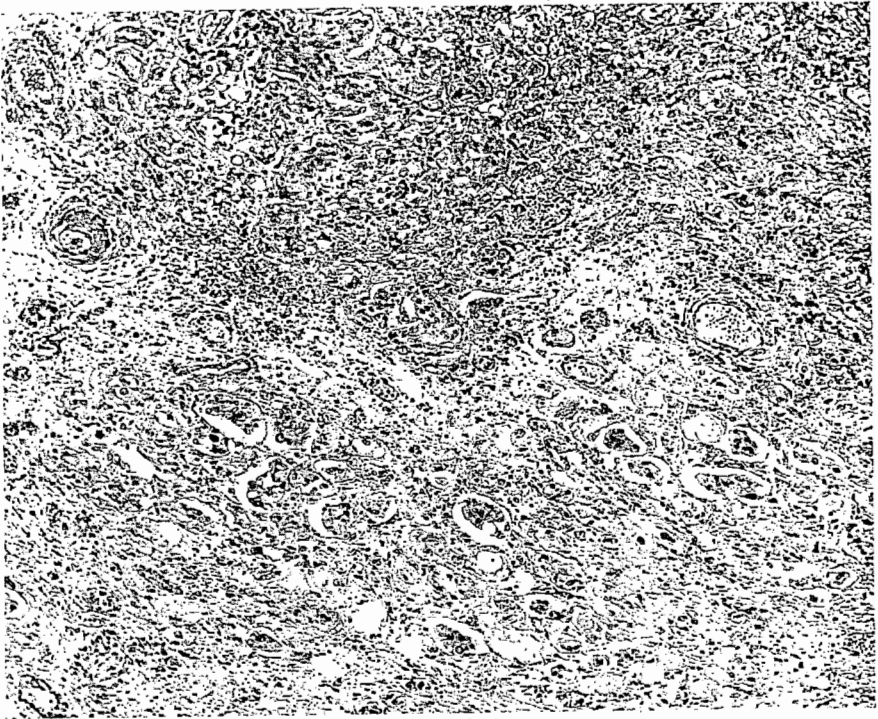


FIG. 1. Poorly differentiated squamous carcinoma on surface with many lymphatics involved in submucosa. S. P. 57-5418. $\times 100$.

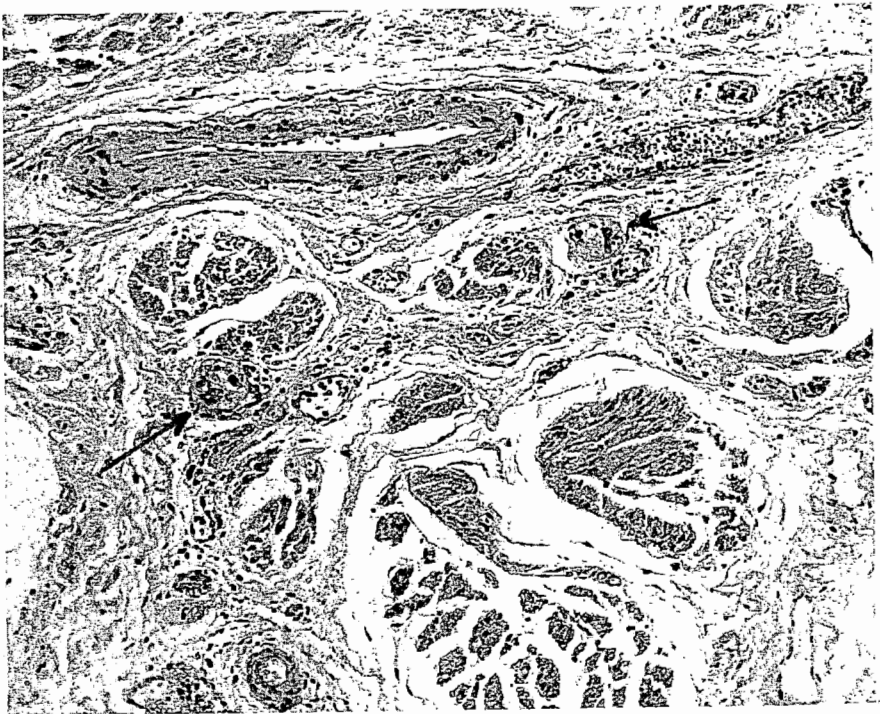


FIG. 2. Same case as figure 1, showing collections of tumor cells within two lymphatics in muscularis. $\times 150$.

ship between the level at which the lymphatics were involved and the depth of extension of the associated mass, together with its cellular characteristics, are shown in figure 3.

Stage C was reached by lymphatic metastasis alone in only eight of the 155 cases comprising that group (5 per cent) (fig. 4), and in only five of its 80 poorly differentiated squamous carcinomas (6 per cent). Furthermore stage C was reached by lymphatic spread in only 3 per cent of all superficially infiltrating tumors (table 2), and in only 8 per cent of those that were highly malignant. But it was reached in two of 12, or 17 per cent, of the poorly differentiated squamous

carcinomas confined primarily to stages A and B₁ (table 3). Local lymphatics involved at different levels were as follows: stage A, one in 40 (2.5 per cent); Stage B₁, six in 22 (28 per cent); Stage B₂, 14 in 35 (40 per cent); stage C, 66 in 155 cases (40 per cent) (table 4). These reported levels at which lymphatic involvement was demonstrable included some cases in which the penetration of the primary tumor mass had lagged behind the more rapidly spreading lymphatic metastases. Although the figures show that lymphatics are more frequently involved by tumors that are deep in the bladder wall, it seems likely that intramural lymphatic metastasis would be found more often at all levels if serial sections could be made in each case. Such an undertaking, however, is obviously not practicable. In the biopsy specimens lymphatic involvement always should be searched for, especially when the tumor is believed to be only superficially infiltrating and to consist of poorly differentiated squamous carcinoma.

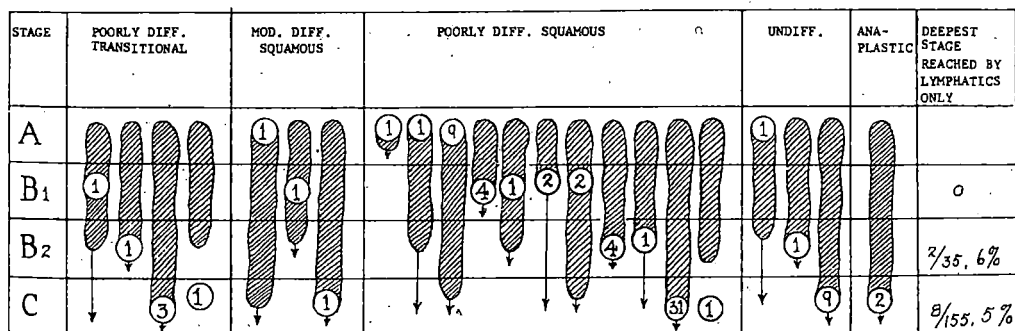
The second source of error leading to the preoperative miscalculation regarding the true extent of infiltration is also related to the manner in which the tumor invades the bladder wall. Slender finger-like projections of tumor may extend for considerable distances from the primary mass and, when cut at right angles to their axis, appear as isolated masses or nests (fig. 5). If such a strand of tumor takes a tortuous course through the wall, its continuity can be recognized only by serial sections, and a single section might show a solitary clump or nest at some distance from the primary growth.

TABLE 1. Classification of 252 cases of infiltrating carcinoma of the bladder

Type of Tumor	Stage of Infiltration				
	A	B ₁	B ₂	C	Total
Well diff. trans.....	11	0	0	0	11
Mod. diff. trans.....	13	10	4	9	36
Poorly diff. trans.....	8	4	6	16	34
Mod. diff. squam.....	0	3	7	16	26
Poorly diff. squam*.....	8	3	14	80	105
Undiff.....	0	1	2	24	27
Anaplastic.....	0		1	7	8
Adeno.....	0	1	1	3	5
Total.....	40	22†	35	155	252

* One additional case consisted of a primary mass at stage B₁ but with a cell nest in stage C. This required final classification as stage C.

† One additional case, noted above, classified as stage C, was primary stage B₁.



LYMPHATIC INVOLVEMENT IN 252 CASES OF INFILTRATING CARCINOMA OF THE BLADDER

KEY: - MAXIMUM DEPTH OF INFILTRATION OF PRIMARY TUMOR.
 - NUMBER OF CASES, AND MOST SUPERFICIAL LEVEL OF LYMPHATIC INVOLVEMENT
 - MAXIMUM DEPTH OF LYMPHATIC INVOLVEMENT

FIG. 3

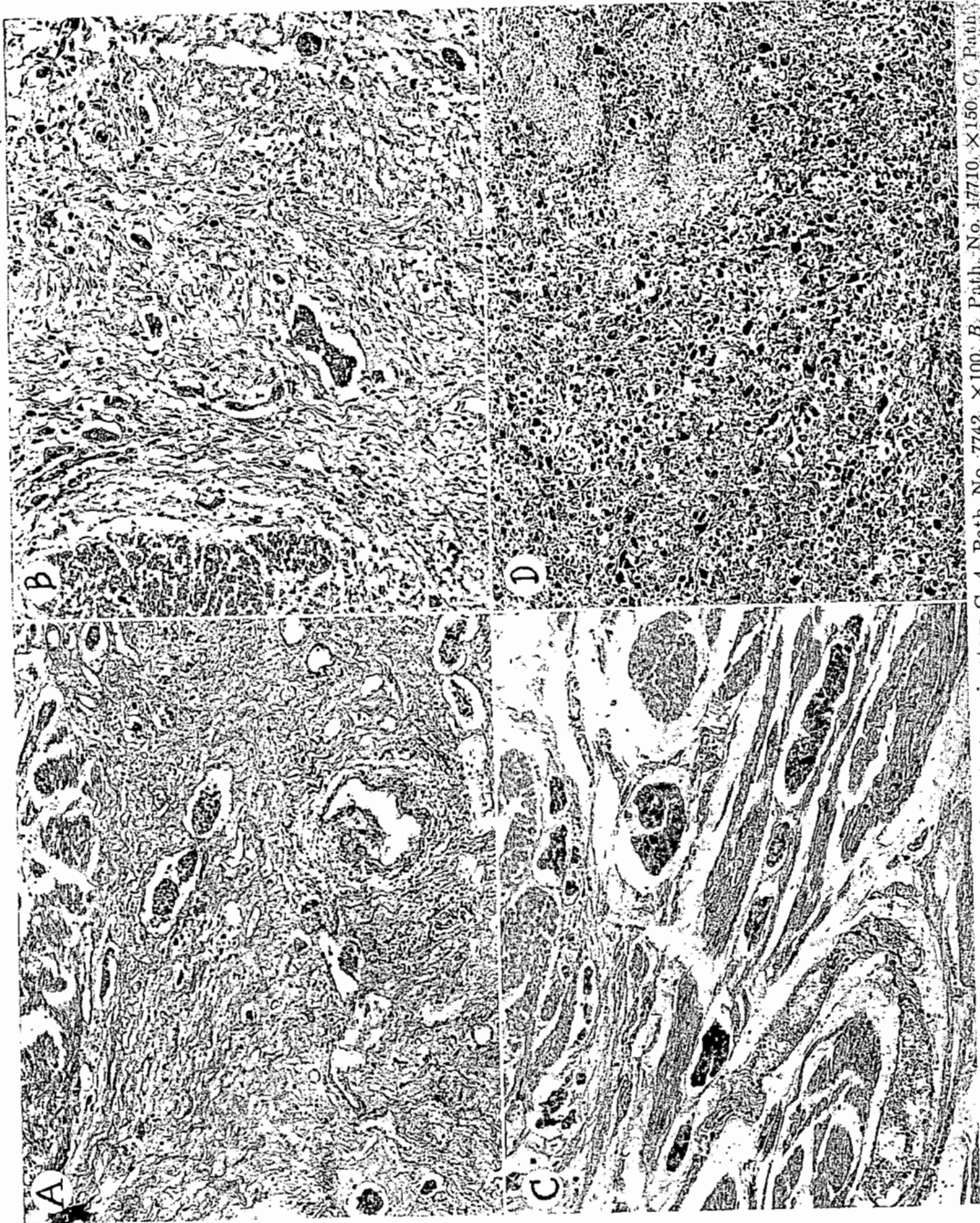


FIG. 4. Deeply infiltrating tumors with lymphatic metastases in stage C. A, Path. No. 7742, X100. B, Path. No. 17710, X150. C, Path. No. 12872, X150. A, B, C, poorly differentiated squamous carcinomas. D, Path. No. 25533, X100. Anaplastic tumor.

TABLE 2. *Lymphatic spread to stage C from tumors in primary stages A and B₁*

Stage	Total Primary Tumors	Stage C	
		No. of cases	Per cent
A	40	0	0
B ₁	23	2	9
Total.....	63	2	3

TABLE 3. *Lymphatic spread to stage C from tumors of high grade in primary stages A and B₁*

Type of Tumor	Total Primary Tumors	Stage C	
		No. of cases	Per cent
High grade.....	26	2	8
Poorly diff. sq.....	12	2	17

Our series of 252 cases were therefore studied to see how often such finger-like projections could be demonstrated and what sort of tumors gave rise to them (table 4). In stage A there was none; in stage B₁ there was one. In one other

case, in which a primary compact mass was in stage B₁, an isolated nest of tumor cells was found in the perivesical fat, apparently not within a lymphatic. This was one of 12 poorly differentiated squamous carcinomas primarily in stage A or B₁ (8 per cent). In stage B₂ there were six, and in one additional case a moderately differentiated transitional cell carcinoma, which appeared compact, was associated with an isolated tumor nest in the fat.

Table 4 represents a summary of the three characteristic ways in which the tumors were found to penetrate the wall of the bladder. The tendency was for most of them to invade as a more or less compact mass with no significant separation of small clumps or single cells in any direction from the main tumor (70 per cent of 252 cases) (fig. 6). The chief exception was in cases of poorly differentiated squamous carcinoma that were deeply invasive. Here the characteristic pattern consisted of finger-like projections of invasive tumor, often cut across in such away as to appear in the sections as isolated masses or nests, which in all but a very few cases lay within one or two low power microscopic fields of the main tumor (27 per cent of 252 cases) (fig. 7).

TABLE 4. *Modes of local invasion and maximum penetration by primary tumor. Stage C was also reached by lymphatic metastasis alone in 8 cases and by isolated nests alone in 2 cases*

Type of Tumor	Stage A			Stage B ₁			Stage B ₂			Stage C		
	Solid mass	Strands and nests	With lymphatics	Solid mass	Strands and nests	With lymphatics	Solid mass	Strands and nests	With lymphatics	Solid mass	Strands and nests	With lymphatics
Well diff. trans.....	11											
Mod. diff. trans.....	13			10			4	(1 with nest at C)		8		
Poorly diff. trans.....	8			4			5	1	2	11	3	5
Mod. diff. sq.....				3			7		1	12	4	2
Poorly diff. sq.....	8		1	2	1 (1 with nest at C)	6	10	4	9	31	44	47
Undiff.....				1			2		2	15	10	10
Anaplastic.....								1		6		2
Adeno.....				1			1			3		
Total.....	40	0	1	21	1	6	29	6	14	86	61	66

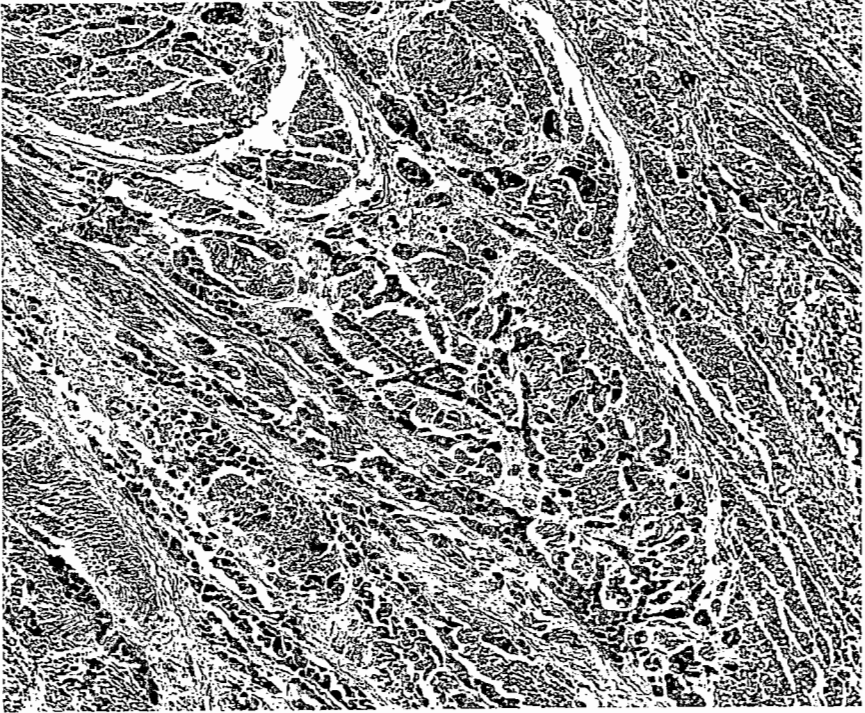


FIG. 5. Poorly differentiated squamous carcinoma with finger-like projections, stage C. Path. No. 25484. $\times 100$.

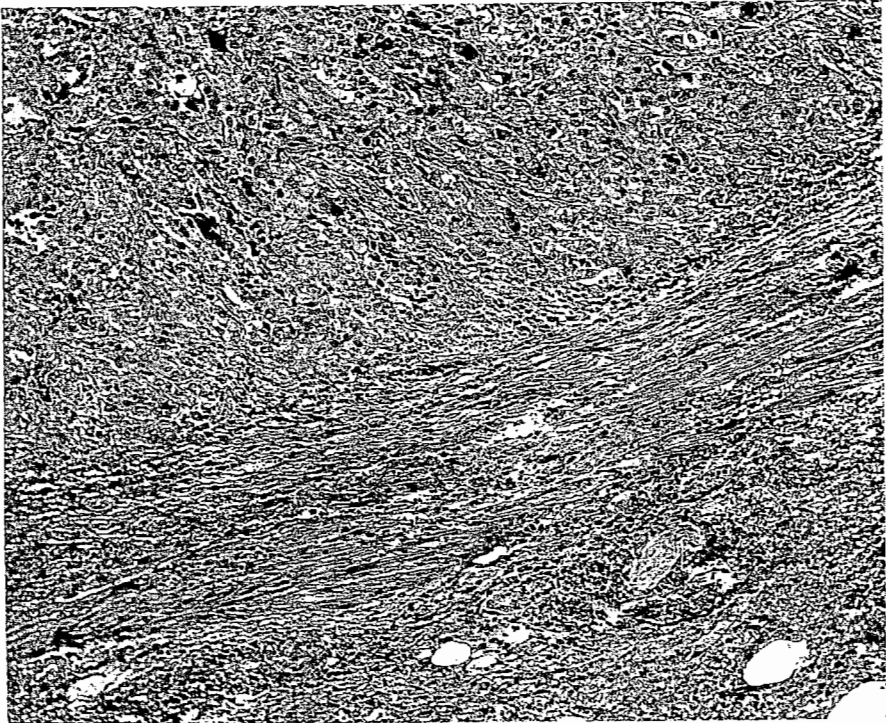


FIG. 6. Poorly differentiated squamous carcinoma. Compact mass. Stage B₂. S. P. 51-102. $\times 100$.

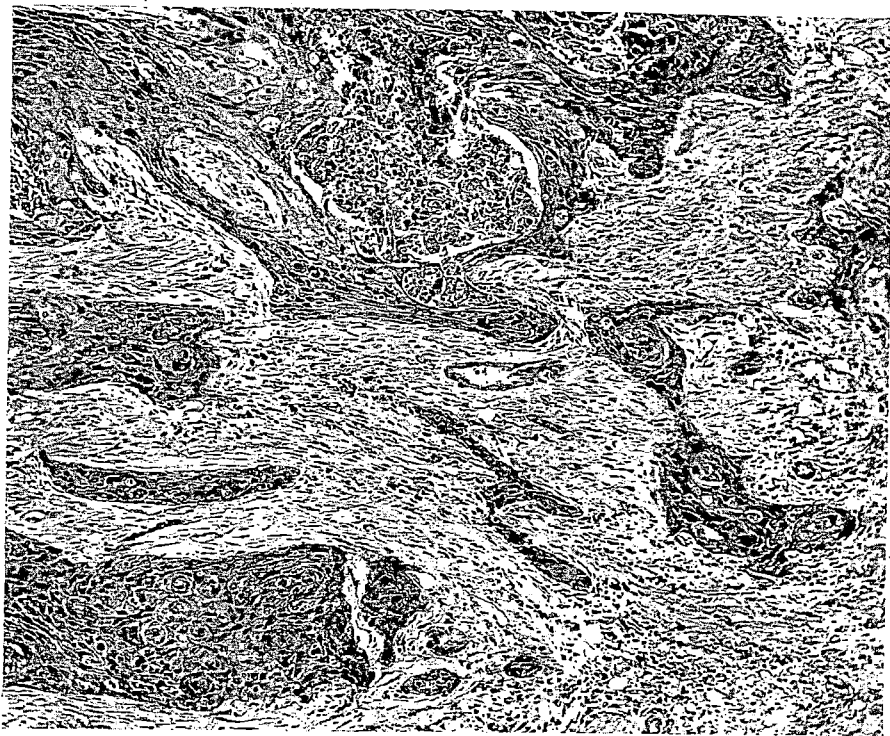


FIG. 7. Moderately differentiated squamous carcinoma. Strands and nests. Stage C. S.P. 55-4488. X100.

The two sources of error, therefore, that make it impossible to predict from biopsy the true extent of invasion by the tumor are 1) intramural lymphatic metastasis and 2) long, slender, irregular projections that do not seem in routine sections to be connected with the overlying tumor. Since the clinical problem in staging is concerned principally with the preoperative separation of tumors in stages A and B₁ from those that are deeper, it is fortunate that these two errors occur only infrequently when the primary mass is superficial. In the present series of 63 cases in which the primary mass was in stage A or B₁, there were only three that had metastasized or extended to the fat. These were of a group of twelve poorly differentiated squamous carcinomas (25 per cent).

SUMMARY AND CONCLUSIONS

The three characteristic modes of local invasion in carcinoma of the bladder are 1) as a fairly compact mass (70 per cent), 2) as finger-like projections represented frequently as isolated masses (27 per cent), and 3) as intramural lymphatic metastases traveling in a direction more or less perpendicular to the plane of the overlying bladder mucosa (3 per cent). Miscalculation in the preoperative estimate of extent of infiltration should be infrequent. It however must be emphasized that when this error does arise it usually will be found among cases exhibiting the last two modes of invasion, especially when the tumor is a poorly differentiated squamous carcinoma.