

Bladder Tumors

A Symposium

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PARTICIPATING INSTITUTIONS

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CURRENT CLINICAL PROBLEMS REGARDING BLADDER TUMORS

VICTOR F. MARSHALL, M.D.

WHILE awaiting some chemotherapeutic solution to the problem of bladder tumors, specifically bladder cancers, or some understanding of their pathogenesis that might assure their prevention, urologists have to treat patients by the means that are presently at their disposal, though these means may appear inadequate. Actually, something worth while can be done for many patients today. But how much? And for which patients? If present methods (and they are far from ideal) are to be modified or new ones devised a base-line of past experience is needed in order to demonstrate the effect of the new therapy. This is particularly true if the new program is likely to produce only small advances instead of the long-hoped-for revolution.

This current problem may be illustrated in the following way: Suppose that a well-trained surgeon without previous experience in the treatment of bladder tumors is suddenly called on to direct the management of a large group of patients with this disease. It is most likely that he would seek to profit from the experience of the past as reported in the literature or by his colleagues. He will think it peculiar to find reports of excellent results after simple fulguration in close proximity to descriptions of much more extensive procedures, such as pelvic exenteration. Implantation of gold radon seeds seemed to produce good results ten or more years ago;¹ yet in more recent times total cystectomy seemed to hold greater interest.^{6, 10} Segmental resection and transurethral excision have their advocates and strong supportive data.¹⁴ A variety of radiation techniques would impress the reader, especially those accompanied by a physicist's mathematical and experimental demonstration that the desired dose could be delivered by the

technique under consideration. The uninitiated surgeon must soon realize that the various reported series probably differ in composition even more than the descriptions reveal. He might even conclude that each vesical growth is a law unto itself. The suggestion has been made that each growth should be described in a full paragraph because only then can the true situation be conveyed. However laudable such effort might be, the outcome would almost certainly be a chaotic mass of facts.

Hence the student will begin to look for some common denominators by which to classify prognostically the various growths in order that some comparisons between different series can be made. The ideal denominator would be a measurable characteristic common to all of these tumors, which characteristic, according to the degree of its presence, would fundamentally indicate the prognosis. Present knowledge does not provide such a measure. Several classifying guides are known, however: the age and sex of the patient; the location, size, and number of growths; the duration of symptoms; etc. The division of these neoplasms into two groups, papillary and infiltrating, is better than no classification, but the reviewer is likely to become confused by the ever-accompanying third category: the tumors that are both papillary and infiltrating. He may further note that there is the occasional growth, such as in situ carcinoma, that is neither papillary nor infiltrating.

The objective estimation of the inherent malignancy of the neoplasm will begin to appear as a possible way out of the dilemma. This measurement is usually made by a system of histological grading that follows the general plan described by Broders.^{3, 4} The reviewer will note that there is a significant relationship between such grading and the outcome; unfortunately, there are significant inconsistencies, too. The grading systems used do vary; for example, histologically benign papilloma is labeled Grade-I cancer in some and kept in a separate category in others. Certainly, calling a papilloma a cancer will improve one's cure rates but will scarcely improve the lot of the

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patient with bladder cancer. One of the strongest arguments for calling papilloma "Grade-I carcinoma" is that histological and clinical cancer subsequently appears vastly more often in those so afflicted than it does in previously normal persons. Neil Beall reviewed 227 consecutive cases at the Memorial Center in which the first biopsy was reported by the pathologists as papilloma. The records were incomplete in thirty-nine (17 per cent). Thirty-eight (20 per cent of the remaining 188) had cancer revealed histologically within six months of the first biopsy. It is most probable that the majority, if not all, of these thirty-eight cases are examples of the inadequacy of these first biopsies. Often the biopsy was desired only to demonstrate the existence of tumor, leaving detailed diagnosis for more satisfactory circumstances after admission to the hospital. Carcinoma was found almost immediately in the majority of these thirty-eight patients; the few exceptions provide little to show that the whole tumor changed its histological characteristics in these brief periods. On the other hand, thirty-two (17 per cent of the 188) had cancer first revealed histologically after six or more months, but before five years, had elapsed from that first biopsy that had revealed papilloma. These thirty-two patients were followed fairly closely during that first six months, usually with equivocal cystoscopic and even biopsy findings. The Papanicolaou test was not then in use.^{16, 18, 19} If those cases in which malignancy was demonstrated histologically within six months are considered to be examples of inadequate biopsy, there still remain the 17 per cent of the 188 cases in which carcinoma was revealed before five years had elapsed since the first biopsy. Incidentally, a common problem in reporting is

where to categorize the case in which the tumor does change its degree of malignancy. To illustrate, it could be argued that all those cases of papilloma in which cancer subsequently appeared do not illustrate the course of papilloma per se and therefore should be removed from the series of papillomas and placed in the carcinoma series. In such a way, the papilloma series can be made to appear quite favorable prognostically. A feature of Beall's study that lends additional support to the significance of histological grading is the fact that subsequent cancer was almost twice as common among those patients who had "papilloma with atypical cells" as among those with histologically pure and simple papilloma (Table 1).

From these data it appears that, of those who have adequate biopsies that reveal simple papilloma according to the criteria used at Memorial Hospital, about one in six patients will have histological evidence of carcinoma within five years. The five-year-death rate of the 138 patients with simple papilloma (21 per cent) was greater than that expected in the general population of similar age (9.4 per cent of the general population at age 56 may be expected to die during the succeeding five years).⁵ Even so, the survival rate for patients with papilloma is so significantly different from that of those with cancer that papilloma is considered by us to be worthy of separate classification. Furthermore, from the viewpoint of the clinician, metastases and invasion are extremely rare while the growth is still histologically benign according to the examination of what is commonly considered to be adequate material. Only two of approximately five hundred cases reviewed showed such metastases and invasion.

The experience at Memorial Hospital and The New York Hospital-Cornell Medical Center also demonstrates in a general manner the prognostic significance of grading among the histologically malignant growths. In Table 2 the five-year survival from the time of diagnosis is outlined for 107 roughly consecutive patients with low grade (Grades I and II) carcinomas; 132 with high grade (Grades III and IV) carcinomas; and the 138 patients with simple papillomas.

These data are presented here to show the considerable differences in outcomes according to histological grades. They are not presented

TABLE 1
ITEMS ON THE SIGNIFICANCE OF A RANDOM
BIOPSY REVEALING "PAPILLOMA"
Memorial Hospital Only; Study by Dr. Neil Beall

	No. pt.	%
Consecutive pt. with first biopsy showing "papilloma"	227	
Inadequate follow-up during 5 yr.	39	17
Adequate follow-up during 5 yr.	188	
Histological ca. found within 6 mo.	38	20
Histological ca. found after 6 mo. and before 60 mo.	32	17
Survived 5 yr. from time of first biopsy showing "papilloma"	108	79
Adequately followed pt. originally with simple papilloma	138	
Histological ca. found within 6 mo.	25	18
Histological ca. found after 6 mo. and before 60 mo.	19	14
Adequately followed pt. originally with atypical papilloma	50	
Histological ca. found within 6 mo.	13	52
Histological ca. found after 6 mo. and before 60 mo.	13	

TABLE 2

SURVIVAL FROM TIME OF DIAGNOSIS, ACCORDING TO HISTOLOGICAL GRADE, DURING AN ERA OF ENTHUSIASM FOR FULGURATION AND RADIATION

	No. pt.	%
<i>Papilloma</i>		
Number of pt. (Beall)	138	
Five-year survivals	108	79.
<i>Low Grade Carcinoma (Grades I and II)</i>		
Number of pt.	107	
Three-year survival (complete data)	43	40.2
Five-year survival (incomplete data)	26+	24.3+]
<i>High Grade Carcinoma (Grades III and IV)</i>		
Number of pt.	132	
Three-year survival (complete data)	20	15.1
Five-year survival (incomplete data)	10+	7.5+]

to indicate the effectiveness of therapy. Actually, many of the patients with simple papilloma did not have radiation therapy; most of the patients who had radon seeds implanted also had superficial excision and fulguration; and nearly half of the patients who had cancer also received external roentgen-ray therapy. In other words, selection was present in these groups and this selection tended to increase the vigor of therapy as the bad qualities of the presenting tumors increased. In addition, patients of this series are not strictly consecutive, either for the total number or for a single group. Patients for whom there was inadequate follow-up data were excluded (as with the 138 cases of simple papilloma). Three years was the criterion of adequate follow-up for the carcinoma groups, and we have a report on every patient for this period. Hence the five-year figure reported here for the carcinoma groups is based on known survival. Actually, however, there could be more, since not all of the patients were followed for five years. On the other hand, these minor variables seem quite incapable of changing the fact that a considerable difference did exist. For example, if the approximately twenty patients with simple papilloma who were treated during the same period as the 138 just reported, but for whom there is inadequate follow-up data, were added to the group and all twenty were considered as dying during the five years, the five-year survival would be 108/158 (68 per cent)—a figure still superior to that observed in those patients with carcinoma. To repeat: the preceding tables are presented to illustrate the difference in prognosis according to histological grading and not to provide data for free interpretations. Many other studies could also

demonstrate this general correlation between grade and prognosis but only one more will be given here. Of 100 consecutive patients undergoing simple total cystectomy for bladder cancer (not papilloma), nineteen (40 per cent) of the forty-seven who had tumors of low grade malignancy survived this treatment without evidence of recurrence for at least two years, while only seven (13 per cent) of the fifty-three with tumors of high grade malignancy did so.

From data such as these, it may be concluded that, for large groups, a significant relationship does exist between the histological grade of malignancy and the prognosis. In the succeeding (except in the one on radical cystectomy because the five-year follow-ups are too few) are reported 198 patients who had low grade carcinomas and 244 who had high grade carcinomas, with a known five-year survival from first symptom of 60 per cent and 25 per cent respectively (this represents a mere lumping of the usable cases reported here). However, it is evident that for any one single grade the range in variation in individual outcomes can be considerable.

In the recent literature there appears an impressive prognostic denominator; namely, the degree of penetration of the bladder wall by the growth. The work of Jewett and Strong, especially, has clearly shown a close relationship between the degree of penetration and the potential curability. Their study was based on 107 autopsy cases, hence constituted partly a theoretical, retrospective assessment of the potential curability of bladder cancer. The variation between groups was large and dramatic; cancer limited to the mucosa and submucosa was theoretically 100 per cent curable; that which had not penetrated beyond the muscle, 86 per cent; and that in the perivesical tissues and lymphatics, 26 per cent. Subsequent reports have borne out this general trend, and the papers that follow also confirm this relationship between penetration and prognosis; for instance, 233 cases are presented here that, from the best available information, presented only superficial penetration (O, A, or B₁ stages, to be described shortly), with 67 per cent five-year survival from first symptom; and 198 cases of penetration beyond the half way level of the muscle (stages B₂, C, or D), with a five-year survival of 20 per cent.

The clinician may properly inquire as to how accurately the depth of penetration can

GRADE	STAGE		
	Superficial	Deep	Metastatic
Papilloma			
Low-grade Carcinoma			
High-grade Carcinoma			
Unusual Types			

FIG. 1. A classification of bladder tumors.

be determined prior to laparotomy or autopsy. The pathological examinations of the specimens removed at 104 consecutive radical cystectomies and/or pelvic exenterations have been compared with the preoperative estimates regarding the degree of penetration.¹¹ This series is not a representative cross section of bladder tumors generally, because these extensive operations were not advised if the disease did not seem severe enough to warrant the attendant risk or if extra-abdominal metastases were known to be present. Within these limits, however, the series probably is representative of fully developed malignant neoplasms of the bladder between these two extremes, for the general policy at that time was to treat this group of neoplasms by radical surgery and since no patients in this particular series were denied radical surgery because of any disease other than that

of the bladder. Defining the mid-level of the muscle layer as the dividing line between the superficial and the deep neoplasms, it was surprising to discover that, relative to this one division, the preoperative estimate was 81 per cent accurate. These preoperative estimates were based on known and readily practiced procedures: appearance and manipulation on cystoscopy; bimanual examination;⁷ accurate biopsies, especially with the resectoscope;¹³ pyelography; and sometimes cystography; as well as the usual general physical examination, including roentgen-ray studies of bones, lungs, etc. Of particular interest in this study was the clinical relationship between the histological grade of malignancy and the depth of penetration. For example, only fourteen of the 104 were exceptions to the general rule that low grade carcinomas are encountered in superficial stages of penetration and high grade carcinomas in deep stages. Furthermore, seven of the fourteen tumors deviated from this rule to the extent of only one substage; that is, they were not quite up to or barely beyond the dividing line. Hence it can be said that in this series the aforementioned rule was grossly deviated from in only seven of the 104 (approximately 7 per cent). Therefore, serious consideration of the grade obtained from an adequate biopsy can improve the accuracy of classifying a neoplasm according to stage; for example, if a growth is estimated to be superficial but the grade is shown by adequate biopsy to be high, the advisability of revising upward the estimate of the degree of penetration should be seriously considered. Also, the reverse situation in which there is a low grade tumor estimated to be in a high stage is worth further thought. In all but one of approximately forty patients with lymph-node metastasis, the primary growth in the bladder had penetrated beyond the mid-level of the muscle. An associated inflammatory reaction does occasionally give the impression by palpation of an extensive neoplasm when actually the growth itself is small.

From the viewpoint of prognosis, the degree of malignancy and the extent to which this attribute has already carried the neoplasm are surely two of the most important characteristics. They can be significantly assayed separately and, because they are closely related in the great majority of clinical cases, a classification based on a consideration of both de-

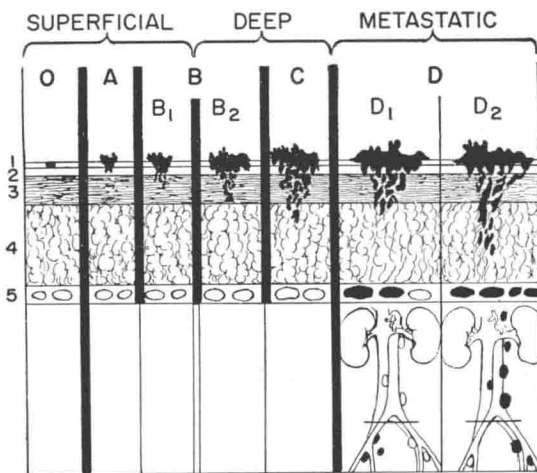


FIG. 2. Stages of bladder tumors. Stage O means that the growth is limited to the mucosa; stage A, to mucosa and submucosa. Stage B indicates muscle invasion (B₁, superficial to the halfway level, and B₂, deep). Stage C is for tumors invading the perivesical fat, and stage D is for those that have metastasized (D₁, if local to the pelvis, and D₂, if beyond). The numbers on the left indicate: 1, mucosa; 2, submucosa; 3, muscle; 4, fat; and 5, lymph nodes.

GRADE	STAGE						
	O	A	B ₁	B ₂	C	D ₁	D ₂
Papilloma							
Grade I							
Grade II							
Grade III							
Grade IV							
Unusual Types							

FIG. 3. Detailed dual classification of bladder tumors.

nominators should increase accuracy in practical application.

The classification used in the succeeding articles is illustrated in Fig. 1. As indicated earlier, superficial or low stage denotes penetration of the tumor up to and including the mid-level of the muscle; deep, past the mid-level of the muscle but without metastases; and metastatic, with metastases and/or invasion of the substance of adjacent organs. The term "high stage" includes any growth beyond the half-level of the muscle layer, deep or metastatic. Later, if it seems worth while to use finer subdivisions, the plan illustrated in Fig. 2 could be utilized for staging. In addition, the grading could be expanded and thus a detailed classification would result (Fig. 3).

Stage O is, of course, a superficial stage. It includes in situ or intraepithelial carcinomas and those cancers in which, although there has been biopsy proof of the existence of the tumor within thirty days of surgical removal of the definitive specimen, no tumor can be found microscopically in that specimen; for example, a tumor was widely excised transurethrally, the biopsy showed definite carcinoma, but no tumor was found when the entire bladder was resected within the next thirty days. Such a situation calls for a classification of stage O, since one could scarcely class a patient as cured on the basis of a thirty-day survival; cancer had been present within thirty days, hence, for the purpose of classification, the tumor was presumed to exist but without demonstrable extent.

In the following papers are reported to a variable degree 1065 cases of microscopically proved bladder cancer from the files of The New York and Memorial hospitals. It should be pointed out that the number of cases is somewhat greater than the number of patients, because the broad statistics that follow are derived principally from the various data from

each of the studies. For example, a patient who was treated at either of the hospitals in two different ways at different times will be represented here as two cases. This seems permissible, if so pointed out, since, if a patient had been treated for biopsy-proved tumor at another institution at another time before coming to our clinics, his would certainly be counted as an individual case.

The oldest patient was 85 years of age; the youngest, 24 (not included are several infants who had sarcoma of the bladder). The average age was approximately 59.5 years. From the time of treatment in the 377 cases of bladder cancer (not papilloma) in which local excision, simple segmental resection, or simple total cystectomy was employed, the survival was as follows: 269 (71 per cent) for one year; 218 (58 per cent) for two years; 191 (51 per cent) for three years; 178 (47 per cent) for four years; and 159 (42 per cent) for five or more years. From the time of first symptom in the 436 cases of bladder cancer in which no treatment, local excision, simple segmental resection, or simple total cystectomy was employed and in which the five-year survival was known, the survival was as follows: 356 (82 per cent) for one year; 297 (68 per cent) for two years; 253 (58 per cent) for three years; 227 (52 per cent) for four years; and 199 (46 per cent) for five or more years. The five-year survival was unknown in only fifteen (3.3 per cent) of the whole group of 451 cases. In the general population the expectancy to survive at 59 years of age is as follows: 98 per cent for one year; 96 per cent for two years; 94 per cent for three years; 92 per cent for four years; and 89 per cent for five years. These statistics are por-

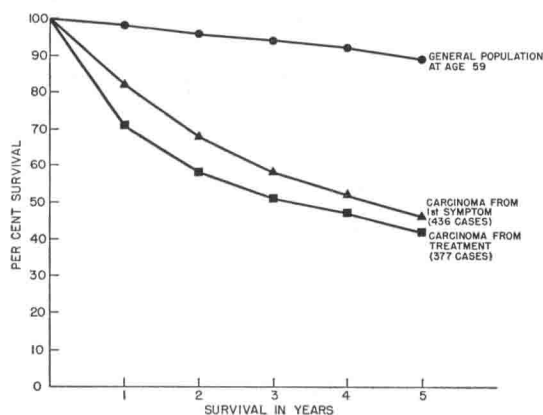


FIG. 4. Survival in the general population and in certain cases of bladder cancer.

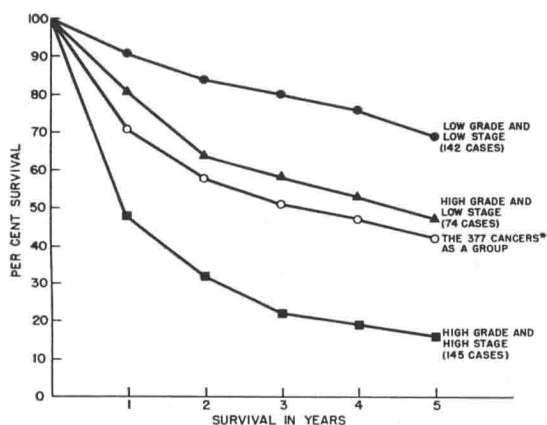


FIG. 5. Survival from treatment according to stage and grade; included are three cases in which grade or stage was not available (see text and Fig. 3).

trayed in Fig. 4 in order to convey some general idea of these survivals.

That grade and stage together are of prognostic value seems indicated from Table 3 and Fig. 5. These show the survivals of patients who had biopsy-demonstrated cancer that was treated by local excision, simple segmental resection, or simple total cystectomy and who had complete follow-up for five years.

The time of first symptom is probably a useful point at which to date the onset of bladder tumor (that is, at least the morphological phase as opposed to the premorphological or generating phase). Usually, the first sign or symptom—hematuria or bladder irritability—is sufficiently dramatic that the patient can recall the date with reasonable accuracy, at least in terms of a few months. An unsuspected and asymptomatic bladder tumor is rarely found clinically. Still more important is the fact that incidentally discovered and previously asymptomatic

bladder tumors are seldom seen at routine autopsies. Charles Olcott of the Department of Pathology at The New York Hospital-Cornell Medical Center reviewed 2805 consecutive autopsies on male patients more than 6 months of age and was unable to discover a single instance. Fred W. Stewart, with an experience well exceeding two thousand autopsies on cancer patients, cannot find or recall an example of incidentally found and previously asymptomatic primary bladder carcinoma. In 1934, the Committee on Carcinoma Registry of the American Urological Association reported concerning 902 cases: "No lesions were seen before symptoms occurred" except in a few patients being examined because of known exposure to a carcinogen in the aniline industry.⁹ From these considerations, it seems clear that the gross forms of bladder tumors are usually not long unheralded. It is not meant to say that these lesions are never found in asymptomatic and nonsuspect circumstances, but rather it is meant to indicate that such is rare. This is, of course, in contradistinction to such growths as carcinoma of the prostate in which long silent periods are well known. From analogy it is certain that the onset of neoplasia antedates the appearance of actual tumor, but at present there is no way of identifying or measuring this process. It is obvious that the desirable comparison of an untreated group with a treated series could not be made if results were measured from treatment; and, if results were measured from positive diagnosis, an incongruity would be present, because treated patients are likely to be first seen either relatively early in the course of the disease or with relatively less malignant

TABLE 3

SURVIVAL FROM TREATMENT OF SURGICALLY TREATED PATIENTS, ACCORDING TO GRADE AND STAGE*

Surv., yr.	Low grade & low stage (142 pt.)		High grade & low stage (74 pt.)		High grade & high or metastatic stage (145 pt.)		Low grade & high or metastatic stage (13 pt.)		Whole series of 377 cancers†	
	No.	%	No.	%	No.	%	No.	%	No.	%
1	129	91	60	81	70	48	7	54	269	71
2	119	84	47	64	46	32	5	38	218	58
3	113	80	43	58	32	22	3	23	191	51
4	108	76	39	53	27	19	3	23	178	47
5	98	69	35	47	23	16	2	15	159	42

*Includes patients treated by local excision, fulguration, simple segmental resection, or simple total cystectomy.

†Grade or stage not available in three cases, so the total of 377 is three more than the simple addition of the first four groups.

TABLE 4
SURVIVAL FROM FIRST SYMPTOM, ACCORDING TO GRADE AND STAGE*

Surv., yr.	Low grade & low stage (79 pt.)		High grade & low stage (32 pt.)		High grade & high or metastatic stage (164 pt.)		Low grade & high or metastatic stage (9 pt.)	
	No.	%	No.	%	No.	%	No.	%
1	72	91	28	88	111	68	7	78
2	63	80	25	78	82	50	7	78
3	61	77	20	63	59	36	6	67
4	61	77	15	44	46	28	5	56
5	56	71	12	37	33	20	4	44

*Includes patients with no treatment and those treated by simple segmental resection or simple total cystectomy (the group is not altogether the same as that in Table 3).

growths. As will be noted in the next paper, the vast majority of the untreated cancers were of both high grade and high stage at the time of diagnosis—in fact, the advanced, hopeless status of the disease was the usual reason for nontreatment. Comparison of the courses of various groups of patients from the time of first symptom might show important differences that could be attributed to the therapeutic modalities; for example, it might reveal that the survival curve of the patients who were treated was turned significantly upward in comparison with that of untreated patients with similar neoplasms.

Among the items to be considered in the outcome, survival is surely one of the most important. Survival can be measured objectively. The estimation of palliation is difficult, complex and often subjective. What constitutes palliation for one patient is not necessarily the same for another.

Table 4 and Fig. 6, which show survival from first symptom, were derived from the summation of the later case material, in which the data are definite regarding survival and in which they appear to be adequate in regard to stage and grade (the tumors were demonstrated to be of AT LEAST the stated degree). The cases from the paper on radical cystectomy were not included, as the five-year follow-up in this series was still incomplete. Also, this particular calculation was not made for the group treated by local excision and fulguration. Again it would seem that the use of both stage and grade increased the accuracy of prognostication.

The cases of 386 men and 100 women with bladder tumors (including papilloma) are reported in the next five papers. The five-year survival after treatment (or diagnosis in the

untreated cases) was somewhat greater for the women than the men; for example, 110 (39 per cent) of 281 men and thirty-seven (45 per cent) of eighty-two women. This particular calculation was not made in the 112 cases of segmental resection, hence the total number here does not equal that given in the first sentence. However, about 4 per cent more white women of age 59 in the general population were expected to survive five years than were men of similar age and color.⁵ It is unlikely, therefore, that the differences in these two series are consequential and it will be noted later that in one series men may survive better, while in another the opposite holds. Calculations were not made to compare men with women using comparable ages and types of tumors; however, for clinical prognostication the differences would seem to be of little use.

Finally, it is significant to note that the patients considered in this and the following

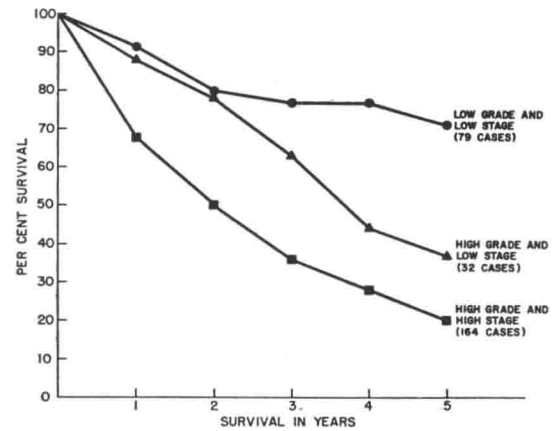


FIG. 6. Survival from first symptom according to grade and stage (see text and Table 4).

papers did come to large, teaching medical centers, one particularly a "cancer" hospital. Hence the proportion of advanced, complicated, or unusual neoplasms is likely to be greater than in the whole universe of bladder tumors. It is known, too, that the patients admitted are not even the full group diagnosed or treated by the staff members; for example, some patients with tiny papillomas have been treated in private offices without admission to the hospital. At the same time, the concentration of fairly large numbers has well-known advantages. So many major and minor variables are present that the reader may well wonder why this study has been undertaken

at all, since every tabulation and conclusion can be questioned on some grounds. Furthermore, the reader will correctly guess that the differences in survival between therapeutic groups will be small—not strikingly and dramatically at odds with all previous experience. However, if nothing whatever can be gained from the rather extensive material at hand, knowing this failure would at least provide grounds for a fresh start.

"No author has a right to claim a settlement of important practical points, on his own bare assertion; to contradict the results of a large and carefully tabulated experience by the citation of one or two cases."¹⁷

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THE PROGNOSIS WITH UNTREATED BLADDER TUMORS

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KNOWLEDGE of the course of patients with untreated neoplasms of the urinary bladder would provide useful comparative data regarding the effectiveness of treatment. Indeed, such information might indicate whether any attempt at therapy is justified. Defining the duration of the disease as the time elapsing from the first symptom to death overcomes some investigative difficulties, as discussed in the preceding paper. Estimation of stage and grade at the time of diagnosis is often hampered by incomplete examinations and records. Limiting the study to autopsies would not only reduce the number of observations but would also introduce a still higher degree of selection. Obtaining follow-up data is not always easy or successful. In spite of these difficulties and because knowledge of even broad trends would be valuable, an attempt to estimate the course of patients with untreated bladder growths on the basis of the best available data seemed worth while.

The records of The New York Hospital from 1932 to 1952 and those of Memorial Hospital from 1926 to 1952 provided sixty-nine examples of bladder tumors in which the patients received either no treatment or treatment that was recognized as inconsequential at the time of administration. Six patients were lost to follow-up. The presence of a neoplasm was clinically evident in three other patients, but histological proof was not available and these have not been included. A review by J. M. Pearce or F. W. Stewart, pathologists, attested to the presence of tumor in all of the other patients. In addition to the nine equivocal cases just indicated, unusual circumstances so masked the neoplastic disease in one other that it, too, was excluded from the study.

A. C. (N. Y. H. 622463) had an infected neurogenic bladder and bilateral hydrone-

phrosis that were related to a transverse myelitis of forty-two years' duration. Death resulted from uremia and sepsis. At autopsy, a transitional-cell carcinoma of the bladder was discovered.

Thus, there remain fifty-nine cases for study. All patients are now known to be dead.

Thirty-eight of the fifty-nine patients received no therapy directed toward control of the neoplasm. Catheterization, vesical lavage, sedatives, and antibacterial drugs were used symptomatically. One previously untreated, moribund patient succumbed to the cancer-produced uremia the same day in which nephrostomy was performed (N. Y. H. 416515), and this case was included. After a detailed review of the individual records, we were convinced that these symptomatic measures did not prolong survival in these patients for so much as six months in any instance; in fact, probably not even for sixty days. Accordingly, survival, as measured by six-month or twelve-month periods, would be affected little. The remaining twenty-one patients did receive some treatment directed against the tumor itself. At the time this therapy was given it could be easily recognized as grossly inadequate so far as having any destructive effect on even the major portion of the cancer. Superficial fulguration of large growths and deep fulguration or excision of clearly less than one third of the lesion was performed in several instances, especially for temporary control of hemorrhage and for biopsy. Eight of the twenty-one received external radiation (N. Y. H. 62467, 411858, and 77963; M. H. 38471 (biopsy B4045 and B5926), J. H. in 1929 [no number found], and 84877). The factors recorded indicate that the dose was far less than any that might be expected to have a significant effect. Thus, at the time of selection of these cases for inclusion in this series, it appeared certain that whatever minor treatment had been given could not have affected survival significantly. Subsequently a comparison with the almost completely untreated group (the thirty-eight receiving only symptomatic attention) showed little variation in

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TABLE 1

SURVIVAL FROM FIRST SYMPTOM OF FIFTY-NINE ESSENTIALLY UNTREATED PATIENTS WITH HISTOLOGICALLY PROVED BLADDER TUMOR

Surv., yr.	No specific treatment (38 pt.)*		Minor treatment (21 pt.)†	
	No.	%	No.	%
1	13	34.2	9	42.9
2	4	10.6	4	19.1
3	3	7.9	1	4.8
4	3	7.9	1	4.8
5 or more	2‡	5.2	0	

*Fourteen (36.8%) failed to survive six months.

†Four (19.1%) failed to survive six months.

‡Both known to have died as a result of bladder neoplasms ten years from onset of symptoms.

survival (Table 1 and Fig. 1). Also, the survival closely paralleled that reported in other series^{2, 7, 8, 10} of untreated patients. No patient in this series received hormones, known anti-cancer chemicals, radioactive materials, or excision of more than one third of the gross lesion. The whole group of fifty-nine will hereafter be referred to as essentially untreated.

The average life expectancy of each patient according to sex and age at onset of symptoms was determined from actuarial tables and the average for the whole group was computed.⁴ Since the incidence of bladder cancer in the general population is low, 7.4 per 100,000,⁵ this calculated survival should be nearly identical with the average expectancy for this group if they had not had a bladder growth. The true survival was catastrophically less (see Table 3 and Fig. 2). Although the women were a little older than the men at the onset of symptoms (an average age of 66 years compared to 63.5 years), they did survive faintly better (see Table 4). If this series of essentially untreated patients is representative, the survival is so short of the expected rate that an attempt at therapy is surely worthy of consideration.

The most frequent reason for nontreatment was that the presenting clinical situation strongly suggested a poor prognosis. Not only the thirty-four listed in Table 2 as having clinically inoperable tumors or prohibitively poor general conditions but probably also most of the eight listed as having incomplete records in these matters had tumors that usually indicate a brief survival. Analysis of all the available data on as objective a basis as possible (obviously excluding the subse-

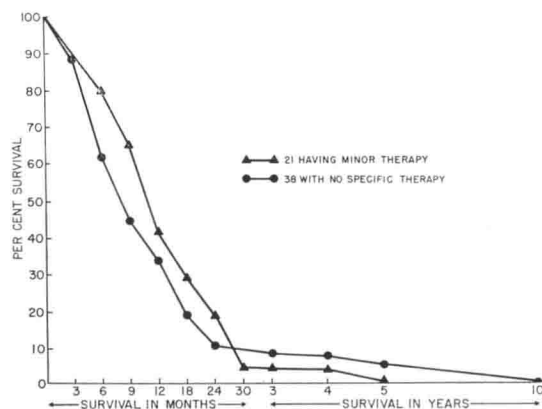


FIG. 1. Survival from first symptom of fifty-nine patients with bladder tumor, receiving essentially no therapy.

quently known prognosis) revealed that the majority of these fifty-nine patients had extensive and/or highly malignant growths at the time of diagnosis. Thirty-seven patients had tumors demonstrated histologically to be of a high grade of malignancy (III or IV) and to be almost certainly at or beyond stage B₂. Whenever the estimation of exact stage was difficult, we made a conscious attempt to classify the growth in the more advanced stage, since previous experience has shown that underestimation is more likely than overestimation.⁶ The survival of these thirty-seven is shown in Table 5 and Fig. 3. The advanced nature of the disease at the time of diagnosis is further revealed by the fact that even though one third of the whole group of fifty-nine were not studied by pyelography, 49 per cent of the fifty-nine were known to have had poor function or hydronephrosis, at least unilaterally. Two patients had vesicovaginal fistulas, and among the others were those who had pleural fluid containing neoplastic cells or pulmonary metastases or metastases in the lumbar spine and pelvis. From these considerations, the survival rate for this whole group of essentially untreated patients is mainly a reflection of the highly malignant nature of the tumors and is not representative for patients having low grade and low stage growths.

The patients who had low grade (I and II) and low stage (O, A, or B₁) lesions at the time of diagnosis were so few that we can do little more than record the survivals. The same is true of the patients who had high-grade (III and IV) tumors found in low stages (Table 6).

Omitting the single example of histologically benign papilloma in this series, there were only eight cases of low grade cancer (13.6

per cent of the fifty-nine). Grading was not possible in two cases (3.4 per cent), but forty-eight (81.4 per cent) were of a high grade histological malignancy. The survival of these groups is shown in Table 7.

The records regarding the tumors in fifty-six patients indicated with seemingly good reliability that the growth was superficial to the halfway level of the muscle in fifteen and had penetrated beyond that in forty-one. The survival of these groups is given both from the time of onset of symptoms and from the time of diagnosis in Table 8. Incidentally, the

TABLE 2
ESSENTIALLY UNTREATED BLADDER TUMORS AT THE NEW YORK AND MEMORIAL HOSPITALS

	No.	%
Total Records Found	69	
Lost to follow-up	6	
No biopsy	3	
Neurogenic bladder masking course of neoplasm, as described	1	
	—	—10
Group for Study (Follow-up Complete Regarding Survival)	59	100.
Men	38	65.
Women	21	35.
No anticancer therapy	38	65.
Obviously minor therapy (as described)	21	35.
Age, yr., at onset of symptoms		
Youngest	41	
Oldest	85	
Average	64.4	
Median	65.6	
Delay from First Symptom to Diagnosis		
Six months or less	28	47.
> six months	31	53.
> twelve months	13	22.
Reasons for Omission of Definitive Therapy		
Refused	12	
Suicide	2	
	—	14 24.
Inoperable extent of neoplasm	17	29.
Poor general condition	17	29.
Exact reason not evident from record	8	13.
Diagnosis not established until autopsy	3	5.
Estimated Stage and Demonstrated Grade of Neoplasms at Diagnosis*		
1. Stage B ₂ , C, D ₁ or D ₂ ; Grades III or IV	37	62.6
2. Stage B ₂ , C, D ₁ or D ₂ ; Grades I or II	2	3.4
3. Stage O, A or B ₁ ; Grades I or II	6	10.2
4. Stage O, A or B ₁ ; Grades III or IV	9	15.3
5. Staging impossible; Grade IV	2	3.4
6. Stage C; grading impossible (cancer cells identified)	1	1.7
7. Simple papilloma	1	1.7
8. Stage B ₂ ; inadequate biopsy revealing only papilloma (good clinical evidence of malignancy)	1	1.7

*Items 1, 4, and 5 make up the total for Table 7, Grade III or IV; items 2 and 3 make up the total for Table 7, Grade I or II; items 3 and 4 make up the total for Table 6; items 5 and 7 not included in total for Table 8; items 6, 7, and 8 not included in total for Table 7.

TABLE 3
SURVIVAL FROM FIRST SYMPTOM OF FIFTY-NINE ESSENTIALLY UNTREATED PATIENTS WITH HISTOLOGICALLY PROVED BLADDER TUMORS

Surv., yr.	New York Hospital-Cornell & Memorial Centers*		Calc. av. expect., %
	No.	%	
1	22	37.4	95.6
2	8	14.3	91.3
3	4	7.6	86.9
4	4	7.6	82.6
5	2†	4.2	78.3
Difference in percentage		74.1	
10	0		58.6

* Eighteen (30.3%) failed to survive six months.

† Both are known to have died at tenth year from bladder cancer.

discrepancy between reporting survivals as from diagnosis (or treatment), as opposed to reporting from onset of symptoms, is clearly demonstrated. After the first two years of natural selection, "survival of the fittest" does tend to even the figures, however. It is evident that the stage reached at the time of evaluation did have a bearing on prognosis from that time onward, but, viewed as the whole history of the growth, there was little difference between these two groups. Did the patients with high stage lesions at the time of diagnosis have a longer total survival, a longer prediagnosis course, but a shorter postdiagnosis course than those found to have lesions in a low stage? The chronological data seemed accurate in terms of one month for forty-six patients, and their survival is depicted in Fig. 4. Because of the variation in each group and the discrepancy

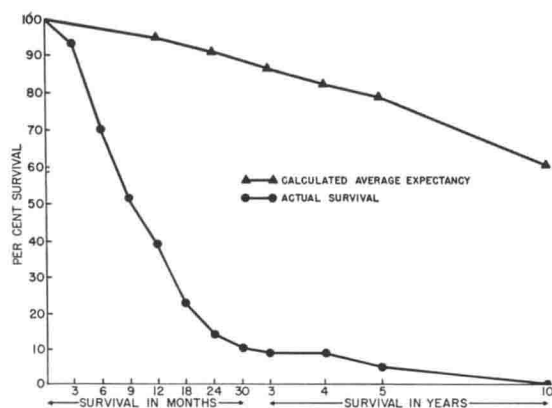


FIG. 2. Survival from first symptom of fifty-nine patients with bladder tumor, receiving essentially no therapy.

TABLE 4
COMPARISON OF SURVIVAL FROM FIRST SYMPTOM OF THIRTY-EIGHT MEN AND TWENTY-ONE WOMEN WITH ESSENTIALLY UNTREATED BLADDER TUMORS

Surv., yr.	38 men*			21 women†		
	Average age 63.5 yr.			Average age 66.0 yr.		
	No.	%	Calc. av. expect., %	No.	%	Calc. av. expect., %
1	13	34.2	95.3	9	43.0	96.1
2	4	10.6	90.7	4	19.2	92.2
Difference in percentage			80.1			73.0
3	1	2.6	86.2	3	14.3	88.2
Difference in percentage			83.6			73.9
4	1	2.6	81.7	3	14.3	84.2
Difference in percentage			79.1			69.9
5 or more	1‡	2.6	77.3	1‡	4.9	80.1
Difference in percentage			74.7			75.2

*Thirteen (34.2%) failed to survive six months.
†Five (23.7%) failed to survive six months.
‡Known to have died at tenth anniversary.

in the size of the two groups, the reader is left to form his own opinion. The possibility that a neoplasm may change its degree of malignancy (grade) must be remembered.

The two examples of ten-year survival from first symptom are at such variance with the general trend that they are outlined here in the following case reports.

E. L. (N. Y. H. 536567) was a 51-year-old white woman who had had intermittent gross hematuria for ten years. Gross hematuria had been constant for three months. A flat, invasive, ulcerated tumor occupied the left lateral wall of the bladder, and a cauliflower growth was present on the opposite wall. Biopsies gave evidence of Grade-IV carcinoma. Bimanually, a stony-hard mass was found to extend beyond the limits of the bladder. The patient refused surgery and died four months later.

TABLE 5
SURVIVAL FROM FIRST SYMPTOM OF THIRTY-SEVEN ESSENTIALLY UNTREATED PATIENTS WHOSE BLADDER CANCERS WERE HISTOLOGICALLY GRADE III OR IV, AND IN STAGE B₂, C, D₁, OR D₂ WHEN DIAGNOSED

Surv., yr.	Surviving				Calc. av. expectancy from first symptom, %
	From diagnosis*		From 1st symptom†		
	No.	%	No.	%	
1	1	2.7	13	35.1	95.2
2	0		5	13.5	90.6
3	0		2	5.4	84.4
4	0		2	5.4	81.4
5	0		1‡	2.7	76.9
10	0		0		55.8

*Thirty-four (91.8%) failed to survive six months.
†Twelve (32.5%) failed to survive six months.
‡Known to have died at tenth anniversary from bladder cancer.

Did she have a slowly progressing tumor for ten years and then develop another neoplasm of greater malignancy? Did the original tumor become more active or did it remain intrinsically the same and merely progress as time permitted?

G. Q. (M. H. 48616) was a 51-year-old white man who had had intermittent gross hematuria for ten years and who had sought no medical aid until acute retention occurred. Cystoscopy revealed a tumor. Catheterization and surgical drainage of a scrotal abscess failed to prevent death from uremia and sepsis. At autopsy a large, histologically benign papiloma without invasion or metastases was demonstrated. This is the only example of a papiloma in this series. Death, though long delayed, resulted from the neoplasm and from the infection developing within it.

Although the immediate precipitating cause

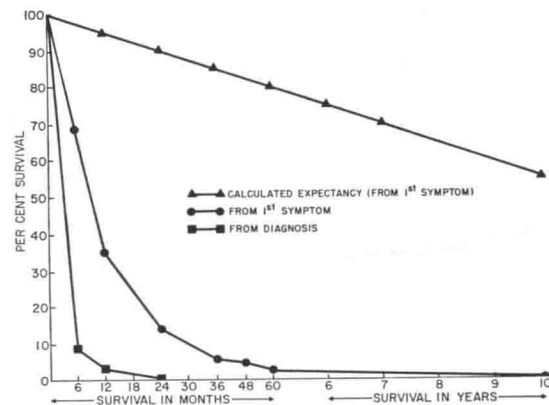


FIG. 3. Survival of thirty-seven essentially untreated patients with high grade and high stage cancer of the bladder.

TABLE 6

SURVIVAL FROM FIRST SYMPTOM OF ESSENTIALLY UNTREATED PATIENTS WITH HISTOLOGICALLY PROVED BLADDER CANCER THAT, ACCORDING TO STAGE AND GRADE, FALLS IN CERTAIN SMALL GROUPS

Surv., yr.	Low grade & low stage (6 pt.)*		High grade & low stage (9 pt.)†	
	No.	%	No.	%
1	1	16.7	6	66.6
2	0		1	11.1
3	0		1	11.1
4	0		1	11.1
5	0		0	

* Three (50%) failed to survive six months.

† One (11.1%) failed to survive six months.

of death is not clearly known in twenty-six cases, there is no suggestion of a spontaneous disappearance of the tumor in any case (Table 9). In the remaining thirty-three cases, the terminal complication is well known (twenty-two autopsies were done). Eleven patients died principally of renal destruction from obstruction and infection. Renal failure and carcinomatosis appeared about equally causative in another six. Thus, dependent renal disease figured prominently in at least seventeen of the thirty-three. Probably more data would have revealed a higher incidence. If three patients who died of vesical hemorrhage are included, eleven appeared to have died because of carcinomatosis rather than general sepsis or renal alteration. Two patients committed suicide; yet, only transurethral therapy was planned for one, and radical surgery had been only barely mentioned to the other. Only three patients (9 per cent) died of unrelated causes: B. W. (N. Y. H. 303402) of lobar pneumonia; B. B. (M. H., Biopsy W7288) and L. L. (N. Y. H. 364389) of cardiovascular disorders. This incidence of death from unrelated causes is exactly what would be anticipated from actuarial calculations (Table 3; Fig. 2).

While the morbidity in this series was unquestionably great, tabulation according to a useful scale would be difficult and would only emphasize the distressing nature of this disease, a fact already evident. No patients were comfortable during their last days, and even those who died from causes other than cancer or bladder disease were not free of symptoms from the bladder tumor. In many instances, the suffering was extreme. The cliché, "The treatment is worse than the disease," certainly should be used infrequently and with caution when referring to bladder cancer.

A review of the literature found systematic reports of survival times of 128 patients with untreated bladder tumors.^{2, 7, 8, 10} From the accompanying descriptions it is evident that the majority had high grade lesions that had reached advanced stages by the time of diagnosis. Most, but not all, had biopsy proof of tumor in the bladder. Our series of fifty-nine closely parallels these others and was added to them (Table 10 and Fig. 5). Nine of the 187 (nearly 5 per cent) survived five years after onset of symptoms, but five of the nine are known to have died before ten years, and one of the remaining four did not have histological proof of tumor. A graph of survival was made from the collected data and was found roughly to parallel a second graph prepared from the data of Welch and Nathanson. Since the latter group is 17 per cent of the size of the former, an approximation of the true survival curve for the whole was constructed by moving the curve of the larger group toward that of the smaller by 17 per cent of the distance between them (Fig. 5). This peculiar maneuver seemed necessary in order to include Welch and Nathanson's valuable series, because their recorded time periods were irregular. Since the exact date of death is not always known, some further variations from the absolute state of affairs are included in this curve, but we estimate that any point probably does not vary from the true by more than plus or minus four months—a matter not serious for the purposes of this study.

Other less detailed reports further attest to the general correctness of these observations. Tuovinen reported seven (24 per cent) of twenty-nine untreated patients surviving one or more years after symptoms or diagnosis but

TABLE 7

SURVIVAL FROM FIRST SYMPTOM OF FIFTY-SIX ESSENTIALLY UNTREATED PATIENTS WITH BLADDER CANCER, ACCORDING TO HISTOLOGICAL GRADE*

Surv., yr.	Grade I or II (8 pt.)†		Grade III or IV (48 pt.)‡	
	No.	%	No.	%
1	1	12.6	20	42.0
2	0		7	14.7
3	0		3	6.3
4	0		3	6.3
5 or more	0		1§	2.1

* See Table 2 for patients not included in this study.

† Five (63%) failed to survive six months.

‡ Thirteen (17.3%) failed to survive six months.

§ Known to have died at tenth anniversary from bladder carcinoma.