The Role of Surgery in the Potentially Curative Treatment of Bladder Carcinoma

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Summary

The surgical procedures that carry the potential for cure for the patient with invasive bladder carcinoma are transurethral resection, segmental resection, various types of cystectomy, and, occasionally, cystostomy with suprapubic fulguration. The success of transurethral resection depends entirely on local ablation, and the reported survival rates suggest that anything more than scant muscle invasion is associated with marked decrease in survival. Segmental resection of invasive tumors suitably placed on the bladder wall are reported to give survival rates equivalent to those for cystectomy. The latter procedure has, in addition to the prevention of further bladder carcinoma, at least the theoretical advantage of removal of the tumor and associated lymphatics. Radical cystectomy, which implies pelvic lymphadenectomy as well, seems to offer a small but definable improvement in survival when a limited number of pelvic nodes are involved. This procedure has been linked to preoperative adjuvant radiotherapy in recent years, and comparisons of survival with historical controls suggest improvement over cystectomy alone. This improvement may be associated with ill-defined factors such as better patient selection, better patient care, and better operative techniques as well as adjuvant radiotherapy. One group of patients that seems singularly advantaged is that in which the adjuvant radiotherapy has left the bladder tumor free. A randomized, controlled study demonstrates improved but not statistically significant survival for the entire group of preoperatively irradiated patients, but analyses support the above: down-staging to absence of tumor provides the greatest success rate. Failures are due to the subsequent appearance of distant metastases in the majority of patients. The lungs and bones seem to be favored sites for the lesions. The evidence suggests that invasion with lymphatic and vascular permeation provides for dissemination of tumor in the majority of patients; thus, invasive bladder carcinoma should be perceived as a systemic disease, and new treatment strategies, including effective systemic chemotherapy and/or immunotherapy, should be given high priority for development.

The intent of this paper is to identify the types of surgical procedures that might be potentially curative in treating patients with invasive bladder carcinoma and, as a corollary, make a judgement regarding these operations. To achieve this objective, one is obliged to collect reports from various sources, identify the form of surgical treatment, accept the estimate of tumor stage and histology, and record a survival figure. Having done so, the urge to discuss these figures becomes almost irresistible. Hence, they shall be discussed before tabulation, rather than after. Thus, the reader is forewarned.

1. Variations in quality of treatment may occur. There are resectionists and there are resectionists, just as there are pelvic surgeons and pelvic surgeons, and different kinds of hospitals and referral patterns.

2. Case selection is an unquantified factor. Skilled physicians often select certain kinds of patients for certain forms of treatment. Few reports inform the reader of the total number of bladder tumor patients admitted to the institution; or of the age, sex, tumor grade, and stage distribution of this group; or of the specific cases selected for a certain mode of treatment. Instead, most reports begin "N patients underwent treatment X," and there then follows an explanation of the characteristics of the population and the disease being treated. Thus, the reports seem to be more about treatment and the disease than about the patients with disease.

3. There is bias in reporting data. This statement is clearly euphemistic in relationship to bladder carcinoma. Most often, only relatively good results are reported. As a corollary, almost no one has poorer survival figures than the authors who went before.

Thus, considering all these variables, one wonders if it would not be appropriate to add ±10% to every survival value. The treatment of bladder carcinoma may not have improved as much as the treatment of the patients; if the mortality rate for radical cystectomy has dropped from 14% (1) to less than 5% (2), the use of historical controls to support the use of new or different methods of treatment, combined or singly, may be inappropriate.

Transurethral Resection and Fulguration of Bladder Carcinomas

Conventionally, one often commences a discussion of this modality with the caveat that the tumor must be localized to the bladder if this form of treatment is to succeed. Emphatically, this is true, and it is very nearly equally as true for all other forms of surgical treatment as well. Since it may be extremely difficult to separate persistent invasive carcinomas from new, invasive carcinomas, the failure rate due...
to incomplete resection of invading carcinomas is not
known. Certainly, the failure rate increases as the size of
tumor and depth of penetration increase, and skill in selec-
tion plays a role in the outcome of treatment.

The results in Table 1 are clear evidence that most resec-
tionists do not do well in curing invasive bladder carcinoma. Barnes et al. (1) and investigators from Iowa (8) seem to be
better resectionists and/or far better selectors of patients.

Barnes has provided us with a denominator: 505 patients
with bladder tumor followed for 5 years, with 410 (81%)
treated by endoscopic surgery. Of these patients treated
endoscopically, the 5-year survival was 53%. Larger tumors
were more likely to be associated with development of
subsequent tumors, and survival was inversely related to
tumor size.

Judgement of transurethral resection of invasive bladder
tumors as potentially curative treatment cannot be made
definitively. It will come as no surprise that patients with
poorly differentiated, deeply invasive, large tumors will be
unsuccessfully treated, or that patients with small, superfi-
cially invasive lesions, especially of a lower grade of differ-
entiation, will probably do relatively well. From the evidence
now available, cystoscopy, cytology, and bladder biopsies
with a cold cup, not a resectoscope loop, taken at random
sites should be consistently negative after initial therapy.

In addition to the problem of the neoplastic diathesis
experienced by many patients with bladder carcinoma,
there is the inescapable fact that clinical staging in associa-
tion with invasive bladder carcinoma is subject to under-
staging by nearly everyone (Refs. 19, 23, and 34; W. F.
Whitmore, personal communication).

Segmental Resection for Invasive Bladder Carcinoma

This form of treatment is hazardous. The patient is often
made to fit the treatment. Its attractive features, e.g., pres-
servation of vesical and sexual function, the ease with which
it can be performed, and the associated scant morbidity and
mortality, lead to its utilization by many physicians when
some other form of treatment would probably be better.

In judging the results of Table 2, some valuable informa-
tion is included, even though some of the patients had
tumors that did not invade muscle. Again, the futility of
comparison of series is demonstrated. Northwestern Uni-
versity urologists (27) seem to be significantly better than
those of the Mayo Clinic (31) if the lesion is B1, but the
reverse occurs if the lesion is deep in the muscle. As the
tumors become more invasive, survival decreases.

In judging this operation, it is evident that good urologists
can select the proper patients for segmental resection and
achieve results that are equivalent to or better than those
obtained, stage for stage, by cystectomy. This may be due
to a variety of circumstances which include position of the
tumor and the scant mortality and morbidity. Furthermore,
there is a suggestion that the tumors suitable for segmental
resection may not have the same virulence as do tumors of
the bladder base. The data of Slack et al. (2) do not support
this rather widely held opinion, yet these patients do seem
to survive better. For selected patients this may indeed be
the best operation.

The following criteria should be met before segmental
resection is carried out. Under those circumstances this
operation will be at least as effective as cystectomy.

1. At least 3 cm of apparently normal bladder are availa-
able to be excised around the tumor.
2. The patient has no history of previous bladder tumor.
3. The tumor is solitary and removal will not require
ureteroneocystostomy.
4. Biopsies of the bladder walls at sites distant from the
tumor reveal normal, not atypical, epithelium.
5. The lesion cannot be managed by transurethral resec-
tion.
6. Adequate bladder capacity is present.

If these criteria cannot be met, cystectomy would seem
indicated.

Radium Implants

Although not strictly surgical, the urologist must play an
essential role in selection of these patients. He has the
responsibility for the cystostomy and for the long-term care
of the patient. After years of careful clinical studies, van der
Werf-Messing (33) and her colleagues in Rotterdam have concluded that the suitable treatment for T2N0M0 lesions, especially those less than 5 cm in diameter, is implantation with radium. Most patients received pre- or postoperative radiotherapy in addition, with a 5-year survival of 60%. This figure for B1 lesions is exceedingly good. The population was highly selected, and histological evidence of muscle invasion was lacking in one-third of the patients. The results are noteworthy. Regrettably, she has not sorted out the results of treatment in those in whom histological evidence of muscle invasion was present.

Cystectomy

Very little was known about the effect of cystectomy on survival of patients with bladder carcinoma until Marshall began a systematic evaluation of the procedure (18). The operation was based on the concept that electroresection and/or implantation of radioactive substances did not control the local and pelvic extensions of bladder carcinoma. Since it was believed that local pelvic disease, i.e., hemorrhage, ureteral obstruction, infection, was clearly responsible for morbidity and mortality (18), the logical step was to remove all of the bladder. Additionally, there was the Brunschwig philosophy that an effective operation for a pelvic carcinoma should follow the pelvic walls where possible, removing peritoneum, lymph nodes, and fat associated with the offending organ. During this same period Jewett and Strong (13) established the clear relationship between the depth of invasion of the bladder wall, lymph node involvement, and curability. Marshall et al. (19) later documented this in the surgical specimens of 104 patients who had undergone radical cystectomy.

From these and other contemporary experiences, 3 guiding principles emerged. Superficial tumors very infrequently became metastatic, those involving muscle were associated with positive nodes in about half of the cases, and positive nodes were tantamount to surgical failure and death. Thus began the long and continuing preoccupation of the urologist with nodal metastases, and most discussions of radical surgery from that time on have concentrated on the status of the pelvic nodes. To be sure, their involvement is a very important matter, but a review of the data currently available suggests that, from a biological standpoint, the initiation of the lethal process begins with muscle invasion. The strongly held concept that pelvic nodes are a 1st-stop phenomenon is not uniformly correct. Current data (Ref. 23; G. R. Prout, Jr., and P. P. Griffin, unpublished observations; W. F. Whitmore, unpublished observations) suggest that hematogenous dissemination plays an essential role in the demise of the host.

Cystectomy in its various total forms produces survival in direct relation to depth of invasion (Table 3). Here the system of staging is that of Jewett and Strong (13) and Marshall (19). A “TNM” system waits in the wings (24) and may improve communication among investigators.

Radiotherapy as an Adjuvant to Cystectomy

Because of the unsatisfactory results of cystectomy alone, a number of urologists and radiotherapists (Refs. 6, 9, 10, 23, 29, 30, and 32; W. F. Whitmore, personal communication) almost simultaneously commenced treating patients with various radiotherapeutic regimens followed by cystectomy. Evaluation of the results of these studies is very difficult. Not only must one make allowances for the many variables already mentioned, but 2 more enter the process. Radiotherapy in most series has been administered at 4000- to 5000-rad levels, and down-staging of the tumors has resulted in about 65% of the patients with invasive carcinoma. This, coupled with the fact that clinical staging is imprecise (Table 4), makes judgement of the effectiveness of adjuvant radiotherapy little more than an estimate. Only 1 common factor, that of histological proof of muscle invasion, can be used to make this estimate, and a clear statement is not always present in the reports reviewed.

Table 5 cites some of the larger series with 5-year follow-up information available. The data from the Surgical Adjuvant Group (32) are pooled information from a number of centers using a prospective protocol that incorporated only patients with proven muscle invasion. The patients were randomized to cystectomy or radiotherapy (4500 rads) followed by cystectomy. This group experienced considerable difficulty in the conduction of the study, and appreciable numbers of patients were excluded from the analyses. The various subgroups have all been described in detail, however (23).

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G. R. Prout, Jr.

Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage (%)</th>
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<tbody>
<tr>
<td></td>
<td>O</td>
</tr>
<tr>
<td>Flocks (8)</td>
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<tr>
<td>Marshall and Holden (20)</td>
<td>62</td>
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<tr>
<td>Jewett (12)</td>
<td>70</td>
</tr>
<tr>
<td>Riches (28)</td>
<td>58</td>
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<td>Resnick and O’Connor (27)</td>
<td>75</td>
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<td>Utz et al. (31)</td>
<td>68</td>
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Table 3

<table>
<thead>
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<th>Study</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
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<td>Brice et al. (4)</td>
<td>37</td>
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<tr>
<td>Bowles and Cordonnier (2)</td>
<td>55</td>
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<tr>
<td>Jewett (12)</td>
<td>50</td>
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<tr>
<td>Wajsman et al. (35)</td>
<td>50</td>
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A comparison of the clinical and pathological stages of patients with bladder carcinoma

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>Pathological stage</th>
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</thead>
<tbody>
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<td></td>
<td>No. of patients</td>
</tr>
<tr>
<td>Varkarakis et al. (34)</td>
<td>( B_1 )</td>
</tr>
<tr>
<td>Whitmore*</td>
<td>( B_1 )</td>
</tr>
<tr>
<td>Prout (23)</td>
<td>( B_1 )</td>
</tr>
</tbody>
</table>

* Personal communication; cystectomy immediately after 2000 rads; therefore downstaging was essentially nonexistent.

Five-year survival of patients with invasive bladder carcinoma treated with preoperative radiotherapy and cystectomy

Assumes all patients had histological proof of muscle invasion.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Survival (%)</th>
<th>Radiotherapy (rads)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van der Werf-Messing (33)</td>
<td>89 (T3)</td>
<td>50</td>
<td>4000</td>
</tr>
<tr>
<td>Reid et al. (26)</td>
<td>92 (&quot;High stage&quot;)</td>
<td>38</td>
<td>2000 (4 days)</td>
</tr>
<tr>
<td>Whitmore*</td>
<td>84 (T2, T3)</td>
<td>42</td>
<td>4000</td>
</tr>
<tr>
<td>Prout (23)</td>
<td>60 (T2, T3)</td>
<td>36</td>
<td>2000 (5 days)</td>
</tr>
</tbody>
</table>

* Personal communication.

Data from this study have relevance regarding the effect of adjuvant radiotherapy. One might expect such treatment to reduce the viability of exfoliated cells and also to reduce the incidence of tumor implantation in the wound. It was an unexpected finding that, regardless of the clinical stage, one-third of the surgical specimens were tumor free. In the cystectomy-only group, the transurethral resection had removed all tumor in the cystectomy specimens in 8%. Hence, 25% of the patients irradiated had their tumors destroyed by what was believed to be a suboptimal dose of radiotherapy.

Another related finding was that deaths occurred rapidly (Chart 1). Only 40% of the patients originally randomized to either arm survived 2 years, demonstrating the lethality of the disease, since nearly all these patients died of bladder carcinoma.

Initial publications indicated no advantage of the adjuvant group because of the previously unappreciated incidence of silent metastases already present at diagnosis or cystectomy. These lethal lesions effectively masked any advantage that radiotherapy might have conferred on the patients, even those whose tumors had apparently been destroyed. Subsequent observation and separate analysis according to the presence or absence of tumor (P+ or P0) demonstrated that an advantage in survival was clearly present in those patients who were P0, whether preoperatively irradiated or not (Chart 2). The improvement in the irradiated P0 patients was statistically significant only when compared to the cystectomy-alone P+ patients. The 11 patients not irradiated who were P0 were very likely patients with largely B1 (T2) lesions in whom the transurethral diagnostic procedure had also been therapeutic.

Van der Werf-Messing (Ref. 33, p. 56) has made similar observations in 89 patients with T3 tumors treated with 4000 rads and cystectomy; "T" reduction is directly related to improvement in survival. When the patients were "P", the actuarial survival was 80% (43 patients), whereas in 27 patients in whom "P" was present (no T reduction) the survival was 17%.
Currently, no suitable system can be used to select patients with radiosensitive tumors. Cell types and even tumor size do not provide good indices. Possibly, the answer lies in the host, and some new and as yet undeveloped study may allow us to predict response.

The matter of metastases is obviously critical. Van der Werf-Messing (Ref. 33, p. 56), in referring to the Rotterdam series, in which all patients received adjuvant radiotherapy, indicates that "If T reduction is achieved . . . death due to lymph node metastases is significantly reduced." The basis for this statement, which may be perfectly valid, is not clear. The cystectomies were all of the simple variety, and no data on nodes are presented in her work. Further, if this were true, one might expect that the patients who were not cured would have evidence of pelvic nodal disease in some high proportion. She makes no mention of this matter.

One might make a case for the possibility that cystectomy produces metastases. Patients in the better survival group had no tumor present in the surgical specimen (Chart 2); hence, no tumor cells could be expressed during cystectomy into lymphatics and small blood vessels, nor could any be implanted intraoperatively.

Bladder carcinoma is clearly a systemic disease in many patients, yet little is known about the 1st metastases in treated patients. We (G. R. Prout, Jr., and P. P. Griffin, unpublished observations) have examined the records of 96 patients who underwent cystectomy for bladder carcinoma at the Massachusetts General Hospital, after September 1, 1969, and not selected by any special criterion. In each patient there was at least knowledge of the histopathological status of the bladder, its covering peritoneum, the pelvic nodes from the bifurcation of the common iliac artery, and (in men) the prostate and (in women) the anterior wall of the vagina and uterus and adnexa if present at operation. The analyses, still incomplete, are shown in Tables 6 and 7.

The 2 patients with tumor in their conduits and ureters did not have new ureteral tumors, since the ureteral mucosa was intact. The patient with retroperitoneal tumor had no pelvic persistence at laparotomy; the tumor had extended to both ureters, obstructing them and producing uremia. He also had bowel and, later, vertebral metastases.

Finally, although all the patients have not been followed for 5 years, of the metastases recorded, 85% have been observed in the 1st year after surgery. Two-thirds of the metastases have occurred in sites other than the soft tissues of the pelvis. One may argue that the ability to detect pelvic metastases in soft tissues is considerably less than one's ability to discover painful bony metastases or silent lesions found on a chest roentgenogram, but subsequent events recorded in the patients' histories do not suggest that pelvic disease was present. Further observations regarding metastases are essential if the course of treated disease is to be better understood. Even with our incomplete knowledge we recognize the great need for effective systemic adjuvant therapy.

Staging of Major Operative Procedures

Transurethral resection, a waiting period for partial healing and subsidence of inflammation, celiotomy and an ileal conduit, another period of convalescence followed by at
least 4 weeks of radiotherapy, followed by another period of recovery, and then cystectomy have been suggested by Mahoney et al. (17) and Grimes et al. (11) as a means of reducing mortality in the management of invasive bladder carcinoma. The studies lack controls and actually do not answer the question of whether mortality is reduced. We [Bredin and Prout (3)] have evaluated the transurethral resection, radiotherapy, and 1-stage cystectomy and conduit approach followed at the Massachusetts General Hospital. In 122 consecutive patients treated for bladder carcinoma between September 1, 1969, and December 31, 1974, we found a mortality rate of 4.1% and appreciable savings in terms of hospital costs and time away from work when compared to the staged approach. Our study also lacks controls, and we can offer only an alternate hypothesis: the cost-benefit ratio is better for the unstaged approach and is not associated with increased mortality. If separate operations for diversion and cystectomy are routinely done, unusual and excessive costs and risks may result without perceptible benefit to the patient.

The conventional approach of 4000 or 5000 rads given preoperatively may also be expensive and time consuming. Both Whitmore (personal communication) and Reid et al. (26) have used smaller amounts of irradiation over short periods of time, and each has reported roughly similar figures. Table 8 records the Memorial Hospital series where Group 1 received 4000 rads and cystectomy after 6 weeks, and Group 2 received 2000 rads in 1 week and cystectomy within 1 week.

Simple versus Radical Cystectomy

There are now 5 reports (Refs. 7, 14, 23, and 26; W. F. Whitmore, personal communication) dealing with significant survival in patients with $D_1$ or $N^+$ disease. These patients, for the most part, would have had disease left behind if simple cystectomy had been used. Because results do not justify dissection to the aortic bifurcation, lymphadenectomy is limited to the midportion of the common iliac vessels. The issue seems settled; radical cystectomy is appreciably more tedious and time consuming, but a perceptible yield in survival is evident. With either technique, the prostate and seminal vesicles should be removed.

When adjuvant radiotherapy has been given, the urologist must have precise knowledge of the fields, the duration of treatment, and the dose given. The bowel segment selected for diversion should be high and short, and the ureters should be tagged and frozen sections obtained to be certain the mucosa is not neoplastic. In young patients, those with diffuse, low-stage disease (especially with flat carcinoma in situ), or a patient who has had a prostatic urethral neoplasm urethrectomy should be done. In others it may be advisable to irrigate the stump with 0.9% NaCl solution at each visit and examine the washing for tumor cells. Any patient who has postoperative urethral bleeding should have his urethra removed unless other circumstances contraindicate this.

### Table 8

<table>
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<th>Tumor extent</th>
<th>Clinical stage</th>
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<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td>No tumor</td>
<td>8/9 (93)</td>
<td>1/1</td>
</tr>
<tr>
<td>IS</td>
<td>8/13 (62)</td>
<td>4/5 (80)</td>
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<td>$A_1$</td>
<td>18/35 (51)</td>
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<td>12/35 (34)</td>
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<td>$D_1$</td>
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<td>1/14 (7)</td>
</tr>
<tr>
<td>$D_2$</td>
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* Group 1 received 4000 rads and cystectomy after 6 weeks; Group 2 received 2000 rads in 1 week and cystectomy within 1 week.

### References


Role of Surgery in Bladder Cancer Treatment

Data from W. F. Whitmore, personal communication.

Five-year survival according to clinical and pathological stage

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