Current Perspectives on Palliative Therapy in Cancer of the Bladder

Bruce H. Stewart and Andrew C. Novick
Department of Urology, Cleveland Clinic Foundation, Cleveland, Ohio 44106

Summary

Palliative therapy eliminates or reduces symptoms in the patient with advanced cancer, with the full knowledge that prognosis is ultimately hopeless. Palliation in general is designed either to relieve local bladder symptoms or to relieve pain or other symptoms related to disseminated metastases. Conservative intravesical therapy by the Helmstein hydrostatic balloon technique or by intravesical formalin appears to be the most effective method for relief of local symptoms without major risk to the patient. Angiocatheter conclusion of the hypogastric arteries may be used as adjunctive therapy in reducing bladder hemorrhage in selected patients. Repeated endoscopic resection and/or fulguration of local tumors can also provide significant palliation if the disease is sufficiently localized. Supravesical diversion with or without palliative cystectomy should be reserved for patients not responding to conservative local therapy. In patients with diffuse pain from systemic metastases, the Brompton protocol has been extremely effective in terms of long-term analgesia and promotion of a sense of well-being. If distant metastases are sufficiently localized, focal irradiation can temporarily relieve local pain or discomfort. Relief of symptoms of uremia in the terminally ill patient with bladder carcinoma should not be recommended except in unusual circumstances. Systemic chemotherapy would theoretically be the most effective method of treatment of systemic metastases, but effective drug therapy is as yet not available for most patients with this disease.

By definition, palliative therapy eliminates or reduces symptoms in the patient with advanced cancer, with the full knowledge that prognosis is ultimately hopeless. Insofar as cancer of the bladder is concerned, elimination of some symptoms (e.g., intractable hemorrhage) may also prolong life in selected cases. In most cases, although life cannot be prolonged, amelioration of severe local or systemic symptoms can be of immense help to both the patients and their families. Relief of ureteral obstruction to prolong life in the face of severe local bladder symptoms or painful distant metastases, however, is false palliation and except in unusual circumstances should not be advised. The cost in both dollars for hospitalization and suffering for the patient is simply too great.

It must be recognized that, despite the plethora of articles on this subject, much of what is reported consists of philosophy and clinical impressions. Hard data on results of purely palliative therapy are often not recorded, base-line controls in terms of natural history and symptomatology are generally not available, and the overall quality of life is usually not taken into account when describing the results of treatment in patients with advanced bladder cancer. Nonetheless, an attempt should be made to summarize the various therapeutic modalities that are now available in the management of these patients and to assess their relative merit in various clinical settings.

Palliative therapy may in general be divided into procedures that relieve severe local bladder symptoms (bleeding, pain, strangury, etc.) and treatment that relieves pain or other symptoms related to disseminated metastatic disease. In addition, there are forms of “palliative therapy” that may actually cure the patient, and this concept will also be discussed. After a review of existing data and an assessment of the relative effectiveness of currently available therapy, a definition of future research needs can hopefully be made.

Palliation for Local Disease

For the patient with severe symptoms due to extensive and incurable cancer of the bladder, the primary goal is to eliminate symptoms and also to preserve bladder function if possible. This of course cannot always be accomplished, and in some cases diversion and/or palliative cystectomy will be necessary to afford the patient maximum comfort for the duration of his life. There are many forms of palliative therapy now available, and experience with each therapeutic modality will herein be summarized.

Conservative Intravesical Therapy

Hydrostatic Pressure Procedures. In 1966, Helmstein (22) developed a new method for treatment of cancer of the urinary bladder, based on the theory that increased intravesical pressure induces a reduction of blood circulation and thus anoxia of the bladder wall. For various reasons tumor tissue is more vulnerable to this form of therapy than is normal bladder mucosa. The procedure has the advantage of relative simplicity and safety with repeated use possible if unsatisfactory results are obtained initially or if re-
currence subsequently takes place. Complications with this form of therapy are uncommon and usually not severe. Rupture of the bladder has been reported but can be prevented with the balloon method and with a decrease in the intraluminal pressure or a reduction in the time of distention. Hemorrhage is rare and can be stopped by rinsing the bladder with e-aminocaproic acid.

With this technique a large rubber ballon attached to a specially designed catheter is introduced into the bladder under regional anesthesia, and the intraluminal pressure is increased to approximately the patient's diastolic blood pressure and maintained at that level for 5 to 7 hr. The treatment has been recommended not only for patients with extensive papillomatosis who have responded poorly to other treatment regimens and for patients with large isolated tumors who are not suited for more extensive surgical intervention but also for patients with highly malignant far-advanced tumors not suitable for curative irradiation or surgical extirpation.

Helmstein's experience with 43 patients indicates that high-grade tumors undergo complete necrosis more than do low-grade tumors; that treatment is more effective when the tumor is located in the region of the trigone, bladder neck, or fundus of the bladder; and that serious changes in bladder function after therapy were not noted. An indwelling catheter is left in place for a few days after treatment, and slight dysuria may persist for a few weeks thereafter (23). Hemorrhage from all types of tumors can usually be controlled by this method of treatment, and significant reduction in bladder-irritative symptoms as well as hematuria can be achieved in the majority of patients with extensive invasive disease (12, 16). Hematuria secondary to cyclophosphamide or radiation therapy can also be controlled by this form of therapy (25). Representative data on the effect of hydrostatic pressure treatment in patients with various stages of bladder carcinoma are presented in Table 1.

**Instillation of Formalin, Phenol, or Silver Nitrate.** The instillation of a 10% formalin solution into the bladder for 15 min under general anesthesia has been advocated by Brown (6) in cases in which palliative total cystectomy for advanced cancer, particularly in patients after earlier deep X-ray therapy, is felt to be contraindicated. With this relatively simple technique, 32 of 36 patients achieved significant relief of hematuria, and 22 or 28 patients noted considerable improvement in strangury for periods averaging 4 to 5 months (5). Excellent results have also been noted by Shah and Albert (48) in 10 of 12 patients receiving 4% formalin instillation into the bladder for control of hematuria secondary to residual bladder cancer, radiation therapy, or hematuria secondary to bone marrow depression as a result of cytotoxic drugs. By their technique a catheter was left in place for 30 min and placed on traction to prevent injury to the urethra by the formalin solution, after which the bladder was drained and rinsed with 10% alcohol followed by irrigation with 0.9% NaCl solution.

Although intravesical formalin therapy is generally free of serious toxicity, at least 1 case has been reported of total bladder necrosis following such treatment. This complication is fortunately rare and should probably not constitute a contraindication for this type of therapy in patients severely symptomatic from hopeless and unresectable bladder neoplasia. The presence of reflux can result in severe ureteral and renal toxicity with intravesical formalin instillation; therefore, a retrograde cystogram should always be done in these patients prior to therapy (A. Melman and J. P. Donohue, personal communication). Insertion of Fogarty balloon catheters to produce lower ureteral obstruction during therapy can prevent this complication. Representative data on the effect of intravesical formalin therapy in patients with inoperable carcinoma of the bladder are presented in Table 2.

The use of intravesical phenol and silver nitrate has also been reported to be of benefit in the control of intractable bladder hemorrhage secondary to either neoplasm or Cytoxan cystitis but does not appear in general to be as effective as the formalin regimen (10, 29, 55).

**Intravesical Chemotherapy.** The intravesical instillation of agents such as thiotepa, bleomycin, Epodyl, or Adriamycin appears to be of benefit in patients with superficial papillary lesions but not of significant benefit in controlling patients with intractable symptoms due to deeply invasive and otherwise inoperable bladder carcinomas (15, 34, 45, 47, 50, 54). It would appear that intravesical chemotherapy is best reserved for those patients with superficial papillary disease either to prevent the frequent recurrence of the disease or to reduce the bulk of the neoplasm so that endoscopic resection and fulguration becomes technically possible. Intravesical chemotherapy could conceivably be considered palliative in the poor-risk patient in whom curative surgical therapy was not possible but in whom a reduction in hematuria and bladder-irritative symptoms was the goal of therapy.

**Intravesical Hyperthermia.** Increasing the intravesical temperature to 41-45° via a 3-way Foley catheter at a rate of 2 liters/hr for 3 hr or 12 days under no anesthesia has appeared to result in local tumor regression in patients with superficial tumors (20), but as yet it has not been assessed as palliative therapy in patients with severe local symptoms due to invasive and otherwise inoperable cancer. Further

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### Table 1

**Response to therapy with hydrostatic intravesical pressure data of Glashan (16)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of patients</th>
<th>Good</th>
<th>Poor</th>
<th>Cure</th>
<th>Improved</th>
<th>Irritable sympotms</th>
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<tr>
<td>T1</td>
<td>9</td>
<td>11</td>
<td>1</td>
<td>9</td>
<td>0</td>
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<tr>
<td>Total</td>
<td>29</td>
<td>28</td>
<td>9</td>
<td>23</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

* One patient was not followed up.

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* C. J. Bergsma and F. J. Leary, Total Bladder Necrosis following Intravesical Formalin. Presented at the North Central Section of the American Urological Association, Palm Beach, Fla., October 18, 1976.
Alternative method to palliative cystectomy and can be used in conjunction with radiation or chemotherapy may be a future possibility. It has been made that the use of heat as a "sensitizer" of this type of therapy will be available, although the suggestion has been made that the use of heat as a "sensitizer" to radiation or chemotherapy may be a future possibility (21).

**Cryotherapy.** Local freezing of deeply invasive neoplasms as an adjunct to palliative transurethral resection has been reported (43). Topical liquid nitrogen therapy via open cystotomy has been reported by MacKenzie (31) as an alternative method to palliative cystectomy and can be used as an adjunct in patients who otherwise require supravesical diversion. This therapeutic modality has been used in patients with intractable hemorrhage due to radiation cystitis, sometimes in conjunction with supravesical diversion. In addition, segmental cryotherapy of isolated infiltrating neoplasms can be used in patients who could not be treated transurethrally and who were otherwise possible candidates for segmental cystectomy. Serious complications including irreversible renal damage from prolonged hypovolemia, inadvertent inclusion of other intraabdominal viscera in the field of hypothermia, and intractable hemorrhage and necrosis of the treated bladder have been reported in patients undergoing this type of therapy. In general, results of cryotherapy purely for palliation have been less impressive than those who do not respond to less toxic forms of intravesical therapy and in whom intractable symptoms persist despite supravesical diversion and hypogastric arterial ligation. Carefully controlled focal cryotherapy as an adjunct to segmental cystectomy in selected cases of localized yet deeply invasive disease deserves further investigation in the future.

**Angiocatheter Techniques**

Arterial infusion of chemotherapeutic agents and/or infarction of the hypogastric arteries by various angiocatheter techniques have been used both for potential cure of invasive carcinoma and for palliation of severe local symptoms. Unfortunately, i.a.\(^6\) infusion of various chemotherapeutic agents has proven to be somewhat cumbersome and has not resulted in a significant cure rate. Some authors (42) have reported a remarkable antimitom effect, although they have admitted that combined operative ther-

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. of cases</th>
<th>Condition improved</th>
<th>Av. period of improvement (mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematuria</td>
<td>36</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Strangury</td>
<td>28</td>
<td>22</td>
<td>5</td>
</tr>
</tbody>
</table>

* The abbreviation used is: i.a., intraarterial.

Data will be necessary before the local and systemic results of this type of therapy will be available, although the suggestion has been made that the use of heat as a "sensitizer" to radiation or chemotherapy may be a future possibility (21).

**Radiation Therapy**

Radiation therapy has been advocated in patients with advanced localized bladder cancer as a potential cure as well as for control of intractable hemorrhage, pain, and bladder irritability. Unfortunately, although abundant data exist on the length of survival and apparent cure rates in patients with both pelvic and distant metastases, there are very few precise data on the palliative effect of such therapy in those patients with local bladder symptoms. In general, although hemorrhage can be significantly improved on a temporary basis in over 50% of patients thus treated, later recurrence is common. Furthermore, pain and bladder irritability are seldom improved and are often worsened by external radiation therapy (18). It would therefore seem wisest to advise external radiation therapy only in the patient with advanced bladder cancer who has undergone prior supravesical diversion. The combined use of 5-fluorouracil and concomitant external radiation therapy has been advised by some authors (27) as potentially curative therapy in patients with various stages of bladder neoplasm, with an early improvement in survival rates noted in potentially curative patients and with some palliation achieved in otherwise hopeless and severely symptomatic patients. As noted by Thomas (52), however, it is disconcerting that there is significant morbidity after radiotherapy, and a surprisingly small number of cases are totally asymptomatic even with apparent cure of their primary neoplasm. Furthermore, overall survival is not improved even in those patients not severely symptomatic from a local standpoint (11). On
the other hand, Woodruff et al. (57) have noted definite regression in 10 of 20 patients with invasive carcinoma metastatic only to pelvic lymph nodes, following a combination of i.v. 5-fluorouracil and concomitant pelvic irradiation with 4000 R. Further study in this field is indicated.

Surgery

**Transurethral Procedures.** Transurethral resection of focal and accessible lesions for control of local irritative symptoms or bleeding is possible in selected cases with known metastatic disease (1). Obviously, most of these patients have deeply invasive tumors that cannot be entirely resected transurethrally, but in many instances the bulk of the tumor can be removed and the patient's symptoms can be satisfactorily controlled by periodical transurethral electroresesection and fulguration. Marshall (32) feels that slow fulguration with a flat electrode with no actual resection is more effective in controlling invasive bladder lesions locally. In his experience, patients treated by slow, long-time heating with a flat electrode do better in terms of both lack of recurrence and length of life than do those treated by standard resection techniques. Furthermore, lesions involving the dome and anterior wall of the bladder are more amenable to therapy by this technique. Obviously, if local symptoms can be controlled by simple endoscopic surgery in patients with metastatic disease, then this form of therapy is preferable to more extensive extirpative or diversionary procedures.

**Palliative Cystectomy.** Total Cystectomy. Total cystectomy in patients with bladder cancer and either local or distant metastases should be considered only if symptoms cannot be controlled by lesser procedures. Since ultimate survival rates are abysmally low regardless of definitive therapy used, that form of treatment should obviously be chosen that will impart the least morbidity to the patient (28). However, Nussbaum (41) makes a very valid point in advising cystectomy, if technically feasible, in selected patients that are suitable candidates for supravesical diversion; the future problems of bleeding and spasm are completely obviated in such patients, and the slight increase in operative morbidity is probably worth it in terms of future palliation. Unfortunately, precise data on the relative merits of total cystectomy vis-à-vis other types of therapy with regard to evaluation of relief of local symptoms, degree of complications, and ultimate length of meaningful life are simply not available.

In general, however, total cystectomy for palliation should be considered only if more conservative measures have failed (49). Most patients in this category have already undergone supravesical diversion after local therapy had failed to relieve severe bladder symptoms. Many have already had radiation therapy to the bladder area or have extensive disease that is invading paravesical structures. Palliative cystectomy in such cases can be technically difficult and can be followed by serious complications; for this reason every attempt should be made to control the patient's symptoms by intravesical instillations and/or angiointerference procedures. If all else has been tried and has failed, the surgeon may have no other choice than to attempt a local resection of the bladder. In this setting a conservative cystectomy should be planned, because removal of the entire neoplastic mass is usually impossible. In patients in whom massive tumor involvement of surrounding structures prevents a reasonably safe cystectomy, simple bilateral hypogastric arterial ligation can sometimes eliminate the problem of intractable bladder hemorrhage.

**Partial Cystectomy.** If the patient has a locally resectable lesion and the remainder of the bladder is normal and if either regional or distant metastases are present, partial cystectomy offers an effective form of palliative therapy. This is particularly true in patients with focal disease and metastases only to pelvic nodes, since the survival rate in this group is extremely low even when radical "curative" surgery is attempted (2, 8, 26, 44, 56). Even in these cases when aggressive surgery is often the popular choice, the old philosophy still prevails that, if there is a choice between a greater or a lesser surgical procedure with approximately the same outcome in length of life, use of the lesser procedure should prevail. If long-term patient survivals through treatment of C or D lesions treated by total versus segmental cystectomy are compared, those patients undergoing segmental cystectomy actually live longer and with far less morbidity than do their counterparts who undergo radical surgery (40). The majority of patients undergoing partial cystectomy for invasive but resectable lesions eventually attain reasonably satisfactory bladder capacity; if the procedure is done properly, the incidence of seeding of the abdominal wound is extremely low. Even in patients with bladder carcinoma involving the abdominal wall, wide resection of the lesion with closure of the resulting defect with omentum and fascia has eliminated the local recurrence in most patients and actually resulted in apparent long-term survival in a few cases (3).

**Supravesical Diversion.** Patients with metastatic disease and intractable bladder symptoms in whom conservative measures have failed are candidates for palliative supravesical diversion. Although the initial symptoms of bleeding, pain, and obstruction can be controlled in the majority of patients thus treated, the well-known complications of supravesical diversion must be borne in mind and weighed against the potential benefit to the patient (7). Although survival time may not be significantly increased in this group of patients, those who survive the procedure without complication can expect significant palliation of local symptoms. Furthermore, urinary diversion may increase the effectiveness of conservative local procedures such as formalin instillation or hypogastric arterial occlusion if these conservative procedures were ineffective in controlling symptoms with an intact and functioning lower urinary system. If the patient is a relatively good risk, has not received radiation therapy, and does not have extensive regional metastases, ileal conduit diversion and palliative cystectomy can be done as a single-stage procedure. However, the mortality rate increases sharply over the age of 70 in such patients and in otherwise poor-risk patients, and in

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this setting simple diversion alone is preferable. In patients
with dilated ureters, cutaneous ureterostomy can be done
more rapidly and with less morbidity than can an ileal con-
duct. Palliative ureterosigmoidostomy should be reserved
for patients with normal upper tracts and normal bowel
function in whom pelvic irradiation is not contemplated.

Unless extenuating circumstances exist, suprapubic di-
version to prolong survival in patients with obstructed ure-
ters and impending death from uremia should not be rec-
ommended. These patients, although their renal function
may recover, subsequently undergo a painful downhill
course with unnecessary anguish and expense to the fami-
lies, and this certainly cannot be considered effective pallia-
tion.

The indications and value of ileal conduit diversion as
palliation for extensive bladder neoplasia is perhaps best
summarized by Yonemoto et al. (58) who stated.

Ileal conduit is indicated as a palliative measure in conjunction
with total cystectomy as a one stage procedure, but only when
severe intractable symptoms exist and only when patients are
carefully selected with regard to age, previous therapy and as-
associated disease. Because of the sudden rise in surgical mortality
in patients over the age of 67 in our series, one is hesitant in carry-
out the procedure in older individuals. Ileal conduit may be
warranted as a preparation to definitive palliative treatment with
chemotherapy or roentgenotherapy. Under these conditions, the
patient has a far better chance of some months or even years of
good active life. Those patients who cannot tolerate a more ex-
tensive curative procedure for medical reasons should also be in-
cluded in this group. Palliative ileal conduit alone performed to
remedy conditions such as urinary fistulas, ureteral obstruction
and malfunctioning rectal bladders, in general, fail to accomplish
adequately the initial objectives listed previously. Best end results
were noted in the patients with urinary fistulas. Although relief of
ureteral obstruction was achieved in 7 of the 8 patients with
advanced pelvic cancer, the average survival of three months
barely justifies the procedure in face of intractable pain suffered
by these patients.

Miscellaneous Surgical Procedures. Less extensive op-
erative procedures, such as hypogastric arterial ligation or
open angiocatheterization with arterial infusion of chemo-
therapeutic drugs, can be carried out in selected patients
(37, 39). Palliation of bladder hemorrhage by these tech-
niques has been reported but is probably less impressive
than that achieved by local hydrostatic or formalin instilla-
tion procedures, which are also simpler and less hazardous.

Percutaneous cordotomy may be indicated in patients
with intractable pelvic pain but without significant bladder-
irritative symptoms or bleeding. Again, common sense
should prevail, and the least traumatic procedure that will
provide the maximum symptomatic relief should always be
chosen.

Palliative Therapy in Bladder Cancer

Palliation of Metastatic Disease or Systemic Symptoms

Chemotherapy and Immunotherapy. Systemic therapy
with various drugs is obviously the major hope not only for
palliation but also for ultimate cure of patients with dissemi-
nated metastases. This subject has been adequately dis-
cussed in another section and will not be further developed
here.

Radiotherapy. Patients with carcinoma of the bladder
who develop focal painful bony metastases can often
achieve significant palliation by relatively short-term radio-
therapy to the areas of discomfort. Three thousand rads are
delivered to the afflicted area for 2 or 3 weeks with standard
megavoltage radiation equipment that delivers 300 rads/treat-
ment until completion of therapy. Symptomatic relief
usually occurs within a few days after institution of therapy
(A. R. Antunez, personal communication). Should diffuse
bony metastases be present, consideration should be given
to the new half-body technique of radiation described by
Fitzpatrick and Rider (13). Initial experience with this tech-
nique is encouraging, although the long-term results are
not yet available and experience in patients with bladder
carcinoma is limited.

Pituitary Ablation. Pituitary ablation by various surgical
and radiotherapeutic techniques has been effective in re-
lieving diffuse pain in selected patients with hormone-de-
dependent neoplasms. Recently, a large-scale experience in
Italy by Morica (35) has indicated that in selected patients
transphenoidal adenolysis of the pituitary gland with alco-
hol can result in significant long-term palliation in patients
with non-hormone-dependent metastatic neoplasms. This
 technique involves passage of a 14-gauge, 5.5-inch stylet-
ted stainless steel needle through 1 nostril via the sphenoid
bone into the sella turcica under light neurolept anesthesia,
aided by radiographic image intensification for precise
needle placement. Particular attention is paid to the rela-
tionship between the anterior and posterior clinoïd pro-
cesses, and 0.6 to 2 ml of absolute alcohol are injected into
the pituitary gland. The procedure may be repeated 1 week
or more later if necessary. It is not yet certain why this
technique should be superior to previous ablative proce-
dures, although recent research suggests a systemic anal-
gesic regulation center in the areas of the hypophyseal stalk
and hypothalamus, which theoretically would be more af-
fected by adenolysis than by conventional ablative proce-
dures. Initial experience in this country is limited but en-
couraging (G. Corssen, personal communication).

Systemic Analgesia. Many patients will eventually de-
velop distant metastases with diffuse pain and gradual deter-
ioration in physical strength. In patients without intolerable
local symptoms in whom extensive metastases are present,
it is questionable whether any form of definitive therapy is
justified (51). In such cases one must simply relieve pain
and make the patient as comfortable as possible during his
terminal illness (33, 53). Perhaps the most effective drug
regimen thus far developed for this type of patient is that of
the Brompton protocol (Table 3). Although generations of
British physicians have gained familiarity with the variants
of the p.o. narcotic mixture bearing the name of the Brompt-
ton Chest Hospital, it was not until 1973 that this formul-
aton was officially recognized in the British Pharmaceutical
Index (4). With the initial institution of this medication, the
patient may be rendered somewhat somnolent and lethargic
but, as the dosage is adjusted, most patients achieve a
relatively pain-free state and are able to maintain reasonably
adequate cerebration. Should pain increase, the dose can
Intracavitary Radiation for in Situ Carcinoma

tion can result not only in significant palliation of the severe potentially lethal lesion curable only by total cystectomy.

Irritative symptoms often accompanying this disease but

However, recent evidence indicates that intracavitary nadia

Amount/dose

Morphine 2.5-150 mg (av. 15 mg)
Ethyl alcohol (98%) 2.5 ml
Cocaine 10 mg
Flavoring syrup 5 ml
Chloroform water AD 20 ml
Phenothiazine syrup or Prochlorperazine
Chlorpromazine

Table 3

Formula for the Brompton mixture (36)

Dosage is 20 ml of morphine solution and 5 ml of phenothiazine solution p.o. every 4 hr (it is recommended that this be given every 4 hr around the clock and not as needed; omit the night dose as needed. The side effects are constipation (treated with 5 Colace and 5 Senekot tablets per day), and drowsiness, nausea, and vomiting, which are usually a problem only in the 1st 48 hr of treatment. The patient receives 20 ml of the mixture every 4 hr. The amount of the mixture given or the frequency of administration does not vary. If the patient is not controlled, then the amount of morphine and/or phenothiazine is increased as necessary until control is achieved.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount/dose</th>
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<tbody>
<tr>
<td>Morphine</td>
<td>2.5-150 mg</td>
</tr>
<tr>
<td>Ethyl alcohol</td>
<td>2.5 ml</td>
</tr>
<tr>
<td>Cocaine</td>
<td>10 mg</td>
</tr>
<tr>
<td>Flavoring syrup</td>
<td>5 ml</td>
</tr>
<tr>
<td>Chloroform</td>
<td>20 ml</td>
</tr>
<tr>
<td>Phenothiazine</td>
<td>5 mg in 5 ml</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
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</table>

be increased, and the patient can at least be kept comfortable during the final phase of his illness. The advantage of this protocol is that it does not require prolonged hospitalization, and self-medication by the patient is possible much of the time (36).

Relief of Uremia. Patients with massively invasive bladder carcinoma may develop lower ureteral obstruction, which if untreated leads to progressive uremia and ultimate demise. In view of the fact that this is usually a relatively painless process and that relief of uremia often results in weeks or months of malaise, increasing pain, and intractable bladder symptoms, it would seem inhumane to relieve the obstruction in most cases. In extraordinary circumstances in which the family or patient wish to prolong life with the full knowledge that it will be uncomfortable and costly, the azotemic state may be reversed by supravesical diversion. If ureteral orifices are visible and accessible endoscopically, intravesical stents may be inserted as described by Gibbons et al. (14) and left indwelling for prolonged periods of time. Occasionally, these stents become obstructed or dislodged and must be replaced; in some cases replacement is not possible. In this event they may be inserted in reverse order by open ureterotomy, placing the base of the stent into the upper ureter or renal pelvis and passing the leading end of the stent downward into the bladder (B. H. Stewart, unpublished data). This procedure, of course, should be considered only in patients without significant bladder symptomatology.

Palliative Therapy That May Actually Cure

Intracavitary Radiation for in Situ Carcinoma

It has been felt by many surgeons that carcinoma in situ is a potentially lethal lesion curable only by total cystectomy. However, recent evidence indicates that intracavitary radiation can result not only in significant palliation of the severe irritative symptoms often accompanying this disease but also in long-term ablation of the disease in the majority of patients thus treated. With this technique a specially designed Foley catheter with a 25-mg radium capsule anchored within the center of its balloon is passed in its deflated state into the bladder under light general anesthesia. The balloon is then inflated with exactly 30 ml of a 5% sodium iodide solution colored with a small amount of methylene blue. During the radium therapy, discoloration of the urine by the dye will indicate accidental rupture of the balloon and will require prompt removal of the catheter. An immediate X-ray is taken to demonstrate symmetrical filling of the balloon with contrast medium, thus ensuring an even distribution of the radiation intensity to the bladder wall. The catheter is left indwelling for 4 days during which time a total of 4000 rads is delivered to the bladder wall, penetrating to an estimated depth of 2 to 3 mm (24).

Since 1965, more than 20 patients with carcinoma in situ have been treated with intracavitary radiation at the Cleveland Clinic Foundation, Cleveland, Ohio. Bladder-irritative symptoms have improved within 1 or 2 months after therapy in most of these patients, and about one-half of the patients have remained asymptomatic and free of recurrent disease for periods of up to 5 years (C. B. Hewitt, personal communication). In those patients who have later developed progressive disease, the radiation effect has been so superficial that cystectomy can still be carried out without technical difficulty and with no increase in morbidity (46).

Diversion and/or Radiotherapy

Patients with deeply invasive carcinoma that has invaded regional pelvic structures have in most cases a lethal disease. Results from radical cystectomy and regional lymphadenectomy for patients in whom the disease is thought to be confined to the bladder and pelvic lymph nodes are still extremely low in terms of ultimate cure. In fact, the operative mortality in most cases may be higher than the expected 5-year survival (9). Many surgeons feel that radical cystectomy and regional lymphadenectomy has no place in the definitive therapy of invasive bladder cancer because the operative mortality and morbidity in those patients with positive nodes exceeds the long-term survival rate and because radical operation can result in unnecessary death in those patients who did not have involvement of the regional lymph nodes. Radiation to pelvic structures with or without supravesical diversion would, therefore, seem to be a more appropriate course of action in those patients with obvious extension of the disease beyond the confines of the bladder. Although there is no good statistical evidence to document this notion, some authorities think that diversion and radiotherapy is more effective in controlling patients with extensive disease localized to the pelvis than an attempt at radical cystectomy with supravesical diversion. This premise is illustrated by the anecdotal case of a patient 48 years old in whom invasive carcinoma was found to involve not only the bladder but also the paravesical soft tissues, the posterior aspect of the symphysis pubis, and the regional lymph nodes. Supravesical diversion was carried out, and a therapeutic course of supervoltage irradiation was given to the pelvic structures. The patient is alive and free of disease 11 years later and, although he has had...
Palliative Therapy in Bladder Cancer

Recurrent pyelonephritis, his renal function is satisfactory. His i.v. pyelogram taken in 1975 is illustrated in Fig. 1.

The need for supravesical diversion has been questioned by other investigators who feel that a combination of i.a. chemotherapy and pelvic irradiation may actually cure a significant percentage of patients with extensive disease that involves the pelvic lymph nodes. The recent work of Nevin and Hoffman (38) is particularly impressive in this regard and deserves further confirmation. In their experience 90% of 15 patients are alive and well 6 to 66 months after treatment with i.a. infusion of 5-fluorouracil in combination with supervoltage irradiation, although most of these patients admittedly did not have demonstrable pelvic lymph node metastases at the time of treatment.

Cystectomy

Radical Cystectomy and Regional Lymphadenectomy. Most authors agree that radical cystectomy and regional lymphadenectomy in the face of pelvic lymph node metastases or prostatic invasion results in long-term survival rates of near 0%. Such therapy must therefore be looked upon as palliative rather than curative. However, Long et al. (30) challenged this concept in a report of 5-year survival rates of over 20% in patients undergoing radical abdominoperineal cystectomy, prostatectomy, and uretrectomy with intraluminal formalin fixation for Stage D disease. With these radical techniques local recurrence of disease was less than it was with conventional operative techniques, and perhaps this approach now deserves further investigation.

Partial Cystectomy. Partial cystectomy likewise has usually been thought of as a palliative procedure, although the "cure rate" for invasive disease with partial cystectomy has actually exceeded that of radical cystectomy in patients with lesions of comparable differentiation and degree of penetration (40). It is conceivable that partial cystectomy in the patient with isolated pelvic lymph node metastases could result in long-term survival or even cure, and certainly all deeply invasive lesions that are amenable to segmental resection should be thus treated because of the relatively low survival rates, even in patients undergoing radical cystectomy, and because of the need to prevent future bladder symptoms. Should the lesion be confined to 1 side of the bladder, pelvic lymphadenectomy on the ipsilateral side should be considered and, in rare cases with only 1 or 2 positive nodes, a cure might be hoped for. Combined radiotherapy and/or i.a. chemotherapy with partial cystectomy could conceivably improve survival rates, and further work here is also necessary.

Future Research Needs

It is obvious from the multiplicity of palliative methods available that no 1 method is totally effective in achieving relief of either severe local symptoms or symptoms related to distant metastases. The development of effective chemotherapeutic agents in the treatment of transitional cell carcinoma of the bladder is of primary importance. Massive efforts are in progress in this regard, and no further comment is necessary at this time.

Of perhaps more immediate importance in the field of palliative therapy for carcinoma of the bladder is the fact that very few data have been accumulated on patients undergoing therapy after they reach the point at which a complete cure is not possible. Although the length of life after palliative therapy has been reported in some instances, reports on the quality of life have rarely been sufficiently stressed. Usually, there is no good answer to the question "Was the palliative therapy really worthwhile in terms of patient comfort, length of survival, and economic factors?" What is needed is better documentation of when a patient becomes incurable and a candidate for palliative therapy, precisely what symptoms or conditions are being treated, and the results of therapy for relief of both symptoms and longevity. Once base-line data of this type have been accumulated with standard forms of therapy, then large-scale cooperative prospective studies with new modalities of therapy both to control local symptoms and to ameliorate systemic disease should be instituted. Hopefully, and perhaps in serendipitous fashion, methods that prove to be effective palliation may in some instances prove to be predecessors to actual curative therapy.

References

Current Perspectives on Palliative Therapy in Cancer of the Bladder

Bruce H. Stewart and Andrew C. Novick


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