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A Comprehensive Protocol for Management of Cancer of the Bilharzial Bladder

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Summary. A randomized clinical trial for the management of bilharzial bladder cancer is presented. A multidisciplinary approach is adopted. The objective of the study is to evaluate the role of adjuvant radiotherapy in improving the results of surgery in deeply infiltrating tumours, and to screen a number of chemotherapeutic agents for their effectiveness in bladder cancer. A large number of cases will be admitted into the study and the results will hopefully help to achieve better results in the management of this disease.

Key words: Bilharziasis - Bladder Cancer - Clinical trial - Irradiation - Surgery - Chemotherapy.

Carcinoma of the Bilharzial Bladder occurs in a relatively young age group. The nodular fungating type is the most common variety (80%). Squamous cell carcinoma, commonly of low grade, accounts for 75% of cases and pelvic node metastases are relatively uncommon (27%) and distant metastases are rare (3%). The majority of cases belong to T3 or T4 clinical stages at time of presentation (4). Therefore radical surgery is the treatment of choice. The operation usually amounts to anterior pelvic exenteration, with a 5-year survival rate of 27% for all stages. Treatment failure is primarily due to local pelvic recurrence. This is understandable in view of the locally advanced clinical stage of the disease.

Carcinoma of the bilharzial bladder is often referred to as a radioresistant tumour. The tumour is bulky and the tissue tolerance is compromised by the presence of long standing inflammatory changes and associated lesions such as strictures, diverticula and stone formation. In a therapeutic trial, only one third of inoperable bladder cancer cases were able to complete the prescribed radical radiotherapy programme (2). Attempts have been made to improve the tolerance to irradiation by using a split course technique to allow the mucosal reaction to subside, regeneration of the damaged bladder mucosa and improvement of the oxygenation of tumour cells.

Preoperative radiotherapy has improved survival in non-bilharzial bladder cancer (6, 7). In the bilharzial cases, some favourable results have recently been reported in a small series of cases (1). In vitro studies show a high rate of cell proliferation even in low grade squamous cell carcinoma of the urinary bladder as reflected by a high labelling index with tritiated thymidine. This finding seems to support the use of preoperative irradiation for these tumours.

Evaluation of the clinical effectiveness of different chemotherapeutic agents in bladder cancer has been largely neglected. Few studies have been reported and the number of cases was limited (3). In bilharzial cancer a preliminary study has been conducted using two drugs, namely Hexamethylmelanine and VM_{26}. The Hexamethylmelamine gave 50% partial response in advanced tumours while VM_{26} was ineffective (5).

In view of the foregoing data, and with the availability of a large number of cases of bilharzial bladder cancer, a multiple-arm protocol was designed to assess, in a well-controlled clinical trial, the merits and limitations of these treatment modalities.

OBJECTIVES

1. The evaluation of adjuvant radiotherapy in improving recurrence rate and long term survival.

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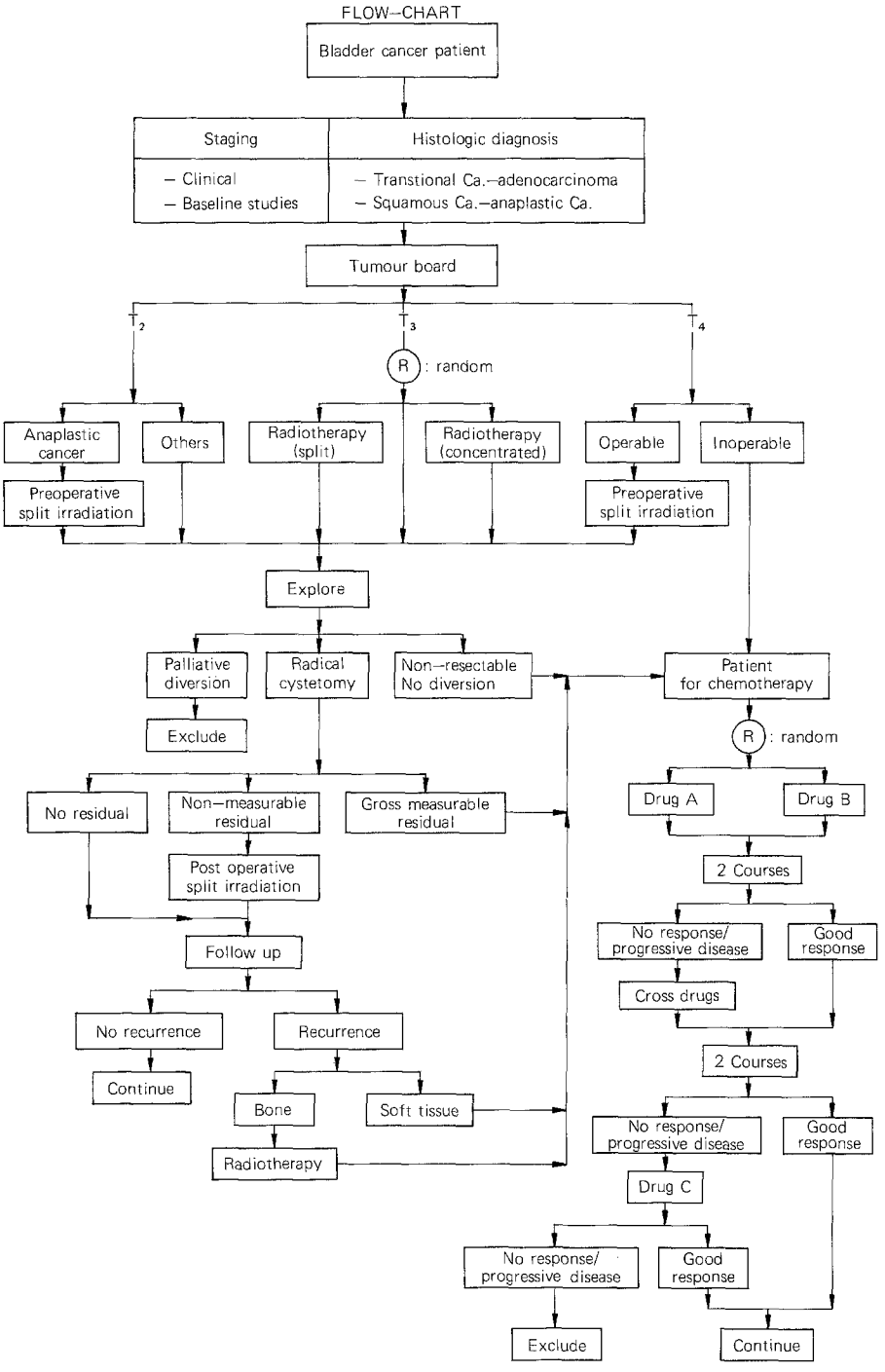
Table 1. Treatment protocol for cancer of the Bilharzial Bladder



2. To screen the activity of various chemotherapeutic agents in various histological types and to correlate the clinical response to cytology.

3. Detailed pathological study of operative material and evaluation of tumour response to preoperative radiotherapy.

4. Detailed study of the cause of post operative morbidity and mortality, including autopsy studies.

5. Detailed study of early and late results of urinary diversion procedures: Ileal conduit, rectal bladder with terminal colostomy, rectal bladder with perineal colostomy, and restorative intestino-urethral anastomosis.

MATERIAL AND METHODS

1. Eligibility

All bladder cancer cases are potential candidates for the study. The following types of patients will be excluded:

a. Past history of anti-cancer therapy.
b. T1 tumours
c. Patients with contraindications to any of the lines of treatment appropriate to the tumour stage.
d. Geographical elimination due to difficulties with follow up.
e. Refusal of the patient to be included in the study.

Every case of suspected bladder cancer will be subjected to complete history and physical examination, followed by routine laboratory investigations for confirmation of diagnosis and staging, and for exclusion of cases unfit for the trial.

2. Case-Accrual

During a five year period, the 1,200 cases are expected (T2 150; T3 700; T4 350).

Once the patient is considered fit for the trial he will be assigned to a line of treatment predetermined in the statistical unit, using the tables of random permutations. Patients with T3 will be randomised into three groups. T4 patients will be divided into two groups (Table 1).

3. Urine Diversion Procedures

Four procedures will be compared, namely ileal conduit, rectal bladder with a terminal colostomy, rectal bladder with a perineal colostomy, and restorative procedures.

4. Pathological Study

a. Surgical Specimen: This will be examined for tumour site, size, grade, stage and node metastases.

b. Autopsy Study: To evaluate causes of immediate postoperative mortality.

DISCUSSION

The results of treatment of deeply infiltrating tumours of the bilharzial bladder cancer have been generally poor. Surgery alone gives a 27% five year survival. If the lymph nodes are involved on one side and the involvement is localised to the obturator group the five year survival is 18%. Comparable results have been obtained in non-bilharzial cases. Radiotherapy alone in deeply infiltrating tumours of the non-bilharzial bladder provide a 10% five year survival (3). In bilharzial cases radiotherapy does not achieve any cures.

It seems logical to adopt a multimodality approach to the treatment of this particular. The present protocol serves to study in one controlled clinical trial, a large number of cases (1,200 cases). The chemotherapy protocol will serve to assess the clinical effectiveness of single agents in advanced tumours. However, in a later phases of the study combinations of effective drugs will be used. Having defined one or more effective combinations, the next objective will be to assess the role of these chemotherapeutic agents as adjuvants to radical cystectomy in operable cases.

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