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NEOADJUVANT RADIOTHERAPY FOR BLADDER CARCINOMA IN EGYPT. PRELIMINARY STUDY ON 56 PATIENTS

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Objective To evaluate the impact of pre-operative accelerated hyperfractionated radiotherapy in the management of bladder carcinoma in Egyptian patients.

Patients and Methods Between December 1996 and February 2000, 104 Egyptian patients with pathologically proven infiltrative bladder carcinoma were enrolled in this prospective study. Patients with all pathological subtypes, non-metastatic disease, clinical stage T2-T4, and medically operable were eligible for this study. A total preoperative dose of 45 Gy was given for an overall duration of 3 weeks, 1.5 Gy/fraction, 2 fractions/day with an interval of 6 hours in between, 5 days/week. Three weeks later, this was followed by radical cystectomy with pelvic node dissection. The clinical radiation response of the tumor was evaluated by C.T. scan done before irradiation and just before surgery. Only 56 patients completed this treatment program. The median follow-up was 26 months, ranging from 9 to 32 months.

Results The actuarial 2-year disease-free survival (DFS) of the 56 patients was 63.9%, with 50% of failures due to pelvic recurrences. The univariate analysis revealed that only lymph node infiltration and pathological staging correlated significantly with DFS. There was a marginally insignificant improvement of DFS among patients who showed an increased tumor regression rate after radiotherapy. The multivariate analysis using the Cox model showed that lymph node infiltration is the only significant predictor for DFS. Other factors including age, sex, cell type, bilharzial infestation and clinical radiation response did not show a significant importance regarding the DFS. Minimal acute radiation toxicity without late tissue reaction was observed among the whole group of patients. No increased operative difficulty related to irradiation nor an increased postoperative morbidity was found.

Conclusion The potential biological advantage of this preoperative radiation schedule (in terms of a shorter overall duration of treatment, a shorter preoperative treatment period, a lower dose per fraction and an overall dose equivalent to conventional fractionation), aiming at an increased tumor regression and a decrease of late normal tissue reaction with its impact on DFS, remains to be further investigated with a larger number of patients and a longer follow-up.

Key Words bladder cancer, bilharziasis, neoadjuvant therapy, radiotherapy

INTRODUCTION

Carcinoma of the bladder is the most common solid tumor in Egypt[1]. Radical cystectomy is the standard treatment adopted in the management of infiltrative carcinoma found in both bilharzial and non-bilharzial bladders[2,3]. In a bilharzial bladder, radical cystectomy offers a 25-32% (5-year) disease free survival rate with most recurrences developing within 24 months postoperatively and being largely local in distribution[4]. In a non-bilharzial bladder, therapeutic outcome with surgery alone has been shown to be disturbingly poor in some cases[5]. Therefore, an adjuvant therapeutic measure is needed to improve the clinical end results. The combination of surgery and pre-operative radiotherapy within an integrated protocol was assumed to improve the final therapeutic yield. Radiobiological evidence of this possibility was provided by several studies[6,7]. In patients with non-bilharzial bladder tumors, a meta-analysis of all trials on preoperative radiation therapy has suggested a survival advantage of only 10%[3]. Similarly, preoperative radiation regimens have been implemented in a number of Egyptian centers, with statistically insignificant improve-

Table 1: Patient Characteristics

Parameter		Number
Age	< 50 years	24
	> 50 years	32
Sex	male	40
	female	16
Pathology	TCC	39
	SCC	17
Grade	2	22
	3	34
LN status	(-ve)	21
	(+ve)	35
Stage (P^o)	P2	18
	P 3, 4	38
Bilharzial Infestation	(+ve)	33
	(-ve)	23
Response to radiotherapy	R	32
	NR	24

TCC = transitional cell carcinoma
SCC = squamous cell carcinoma
(p) = pathological
R = responsive
NR = non-responsive

ment of survival among patients receiving preoperative radiotherapy[4,7]. The fractionated schedules commonly used for preoperative radiotherapy are the conventional long course which delivers 40-50 Gy within 4-5 weeks, followed by cystectomy within 6 weeks and the short accelerated course (20 Gy in 5 daily fractions) followed by surgery within 2 weeks[8,9]. However, a meta-analysis of randomized studies on hyperfractionation (HF), versus conventional fractionation (CF) published since 1980, has demonstrated that HF reduces odds of deaths in patients with bladder cancer to a larger extent than CF[10].

Based on these data and in an attempt to improve clinical end results, the present study was performed to determine the potential value and toxicity of a high dose of an accelerated hyperfractionated schedule of radiotherapy in patients undergoing radical cystectomy.

PATIENTS AND METHODS

Between December 1996 and February 2000, 104 Egyptian patients with pathologically proven infiltrative bladder carcinoma were enrolled in this prospective study. Their age ranged from 40 to 62 years with a mean age of 51 years. All pathological subtypes of the non-metastatic disease including clinical stages T2-T4 and medically operable disease were eligible for the study. All patients were subjected to a complete history and physical examination, complete blood counts and blood chemistry including blood urea nitrogen (BUN), creatinine and liver function tests. Also intravenous urography, bone scan, chest X-ray, bimanual examination under anaesthesia (EUA), pre-treatment cystoscopy and multiple biopsies were done on all patients. CT of the abdomen and pelvis was performed before irradiation and just before surgery. The World Health Organization (WHO) classification of bladder tumors was adopted for histological typing and grading.

Total pelvic irradiation using a linear accelerator 6 MEV machine was applied at a source-skin distance of 100 cm. The target volume included the entire pelvis and extended upward to the level of the lumbo-sacral disc, down to the level of the lower margin of the obturator foramina and laterally to a distance of 1 cm outside the inlet of the true pelvis. Two opposing antero-posterior portals were used during the whole treatment.

A two-fraction-per-day regimen was adopted, the dose per fraction amounting to 150 cGy with a 6-hour interval between fractions. The entire preoperative treatment comprised 15 treatment days, treating 5 days per week and aiming at a total dose of 4500 cGy given in 15 fractions spread over 21 days.

The tumor response was assessed according to the following pattern:

- Post-irradiation tumor response means $\geq$ 50% reduction in tumor size on C.T. scan preceding the surgery.
- Minimal or no response means no change or < 50% tumor regression.

The WHO system was used for scoring acute and late radiation reactions[11]. Late reactions were looked for only in patients who survived 18 months or more.

Radical cystectomy with pelvic lymph node dissection was done 3 weeks after completion of the preoperative radiation. At the time of surgery care was taken to palpate the liver and

Table 2: Analysis of Prognostic Factors

Prognostic Factor		2-Year Actuarial Disease-Free Survival	P Value*
Age	≤ 50	80%	
	> 50	41%	0.43
Sex	male	66%	
	female	67%	0.29
Pathology	TCC	52%	
	SCC	100%	0.60
Grade	II	84%	
	IV	51%	0.21
Stage (Po)	T2	67%	
	T 3,4	56%	0.04
Nodal status	(+ve)	40%	
	(-ve)	85.7%	0.04
Bilharzial infestation	(+ve)	59%	
	(-ve)	100%	0.37
Clinical response	R	65.8%	
	NR	64%	0.80

*P value = Log rank
TCC = Transitional cell carcinoma
SCC = Squamous cell carcinoma
R = Objective response >50% remission of tumor size
NR = No response: <50% regression

the para-aortic lymph nodes prior to bladder dissection so as to evaluate the potential sites of distant metastases. Bilateral pelvic lymph node dissection was then performed meticulously to ensure a good staging after surgery. En-bloc removal of the bladder together with the prostate and seminal vesicles in men or with the uterus and upper part of the vagina in women was then done in the usual way. This was followed by urinary diversion in the form of ileal neobladder in 26 patients (24 males and 2 females), ileal conduit in 22 patients (14 males and 8 females) and uretero-sigmoidostomy "Sigma pouch" in 8 patients (2 males and 6 females). The type of diversion depended on the patient's age, sex, occupation and the condition of the bowel and sphincters.

The World Health Organization and International Society of Urological Pathology (WHO/ISUP) grading system (1998) was adopted for histological classification and grading[12]. The TNM system (1997) was used for pathological staging[13].

Local failure was defined as recurrences in the pelvic surgical bed. Pelvic failure included any local failure and pelvic lymphadenopathy below the bifurcation of the common iliac vessels. Lymph node involvement above this level, in the inguinal region, or haematogenous metastases were defined as distant failures.

The actuarial calculations were started on the last day of radiotherapy. The analysis of survival was done using the Kaplan-Meier method[14]. Log rank tests were applied for comparison between survival curves. The Cox-multivariate analysis was also used for identification of independent prognostic factors[15].

A p-value < 0.05 was considered statistically significant, and all p-values were 2-sided.

RESULTS

Of the 104 patients included in the study, 26 did not complete the planned treatment, because 10 of them were irregular in attending the radiotherapy course, 5 patients developed severe dysuria during irradiation, and 11 patients refused operation after completion of

radiotherapy. In addition to these 26 patients we had 6 patients who had inoperable disease on exploration, 9 were lost during follow up, and 7 were unfit for operation because of liver bilharzial cirrhosis. Finally, a total of 56 patients were evaluated for treatment toxicity and survival. Thirty of them showed pelvic lymphadenopathy on pre-operative CT scanning, but they were still included in the study for the aim of therapeutic lymphadenectomy.

The patient characteristics are summarized in Table 1. Among the 56 patients, the male to female ratio was 2.5 : 1. Median follow-up was 26 months ranging from 9 to 32 months.

There were 39 patients with transitional cell carcinoma and 17 patients with squamous cell carcinoma. Eighteen patients had pathological stage (p) 2, while 38 had stage (p) 3 and 4 tumors. Twenty- two patients had grade-2 tumors and 34 had grade-3 tumors. In 33 patients bilharzial infestation was found, while 35 had infiltrated pelvic lymph nodes. Of these 35 patients, only 25 had positive pelvic lymphadenopathy on preoperative CT scanning. Thirty-two patients showed radiation response of their tumors before surgery.

The 2-year actuarial disease-free survival rate for the whole group of patients was 63.9%.

Treatment failure has been noticed in 16 patients (28.6%). The pelvic failure rate was 21.4% (12 patients) with local failure shown in 8 patients (14.2%) and nodal failure in 6 patients (10.7%). Two patients had local and nodal recurrences and 4 patients had only nodal recurrence. Metastatic failure was observed in 8 patients (14.2%), 4 of them had local recurrence and distant metastases in the liver and the other 4 had bone metastases only.

The univariate analysis of the effect of several prognostic factors on the treatment outcome is shown in Table 2.

Pathological staging and pelvic lymph node infiltration correlated significantly with disease free survival (2-year disease free survival of 67% versus 56% and 85.7% versus 40.0% for both parameters, respectively ($p < 0.05$)).

The Cox multivariate analysis was applied to identify independent individual variables, with the most significant effect on disease-free survival found after elimination of the effect of interaction or dependence between variables. Pelvic lymph node infiltration was shown to be the only significant predictor for disease recurrence. Other factors such as age, sex, cell type, bilharzial infestation and clinical radiation response showed no significant influence on disease-free survival.

Radiation reactions occurred in 24 patients (43%) in the form of grade-1 skin reaction (slight erythema or dry desquamation). Only 2 patients (3.6%) suffered from wet desquamation (G2) at the end of irradiation (at the area of the gluteal cleft). Eight patients (14%) developed tenesmus, which was mild (G1). Thirty-two patients presented with dysuria before radiotherapy, 8 (25%) of them had persistent mild dysuria after receiving proper antibiotics, but 5 (15.6%) patients suffered from severe dysuria during radiotherapy which required interruption of radiotherapy and exclusion of the patients from the study. Of the remaining 24 patients with no pre-irradiation dysuria, only 2 (8.3%) suffered from mild dysuria which was tolerable and did not require interruption of irradiation. No patient showed late radiation reactions.

No major complications were encountered during surgery after irradiation, on the contrary, the field of dissection seemed to be easier in most of the cases and of less bleeding planes. Post-operative complications included ileus in 6 patients (10.7%), prolonged urinary leakage in 10 patients (17.8%), deep venous thrombosis in 4 patients (7.1%) and a mild degree of urinary incontinence in 19 patients (34%) (12 of the ileal neo-bladder cases and 6 of the sigma pouch group). One female with ileal neo-bladder (1.7%) developed attacks of urinary retention and was advised to do clean intermittent catheterization.

DISCUSSION

It is generally agreed that the results of radical cystectomy in bladder cancer need an additional adjuvant local measure to improve its final end result[16,17]. Radiotherapy for cancer of the bilharzial bladder is handicapped by a number of factors. The local tolerance is compromised by the presence of chronic cystitis, ischaemia, ulceration, calcification and other bilharzial lesions. Moreover, most patients present with bulky tumors in which the problem of tumor cell hypoxia is likely to be encountered[18]. An additional treatment to surgery may be in

the form of neoadjuvant or adjuvant radio- or chemotherapy. Theoretically, preoperative radiation renders the tumor cells less viable so that the cells disseminated during surgery are less likely to implant themselves as distant metastases. Also, peripheral micro-extensions of the tumor beyond the reach of the surgical margin may be sterilized and the tumor may be even less bulky. Thus, preoperative radiation may render a technically difficult bulky tumor easier to excise. Accordingly, it was suggested that an integrated therapy would reduce the chance of distant metastases as well as control the high pelvic recurrence rates following radical cystectomy[19].

In initial trials, a preoperative dose of 40 to 50 Gy was delivered to the true pelvis over a period of 4-5 weeks, with cystectomy to follow after 4-6 weeks[8]. Later, a short course of 20 Gy (5 days) was applied; the period between initiation of treatment and cystectomy was shorter (1-2 weeks)[9].

In our study we did not include a control group of patients subjected to cystectomy alone without irradiation, because the survival rates of such patients have been studied extensively before. The well-known published results show that the 5-year survival rate for the muscle invasive disease was 65-82% for stage T2, 37-61% for stage T3. In cases of lymph node infiltration the rate went down to 30%[2,4,5,8].

Parsons and Million (1987) concluded that preoperative radiation therapy appeared to offer a survival advantage over cystectomy alone[20]. This survival advantage is particularly evident among a subgroup of radio-responsive tumors of the T3 category. For low-stage tumors, integrated treatment would offer no therapeutic benefit. Similarly, with advanced disease, preoperative irradiation is not effective because of the presence of extra-pelvic microscopic metastases, which are not within the treated field. This might explain why, when all stages were considered, the therapeutic superiority of preoperative radiation was only marginal and did not show statistical significance[20].

A meta-analysis of all trials suggests a 10% survival advantage, if preoperative irradiation is incorporated. Nevertheless, the putative 10% increment was deemed too small to recommend preoperative radiotherapy for all patients with invasive disease[3].

In the current study we included patients with stages T2-T4. Although T4 is not an indicated stage for radical cystectomy, we tried to study the effect of pre-operative irradiation on the surgical field and whether it will render an inoperable field operable. During the surgical procedures, 6 patients were found to be inoperable on exploration and this was probably due to extensive extravesical infiltration that did not respond to the hyper-fractionated doses of irradiation.

Studies of the growth characteristics of squamous tumors of the bladder disclosed two growth characteristics: a relatively high cell mitotic index corresponding to a potential doubling time of 6 days with an extensive cell loss factor[21]. Tumors with such growth characteristics are expected to show a prompt radiation response. Nevertheless, early experience with external beam therapy for definitive control of these tumors has been disappointing. Several factors interfere with the efficiency of radiotherapy in such patients. Coexisting bilharzial lesions reduce local tissue tolerance. The probability of local tumor control is reduced as a result of their considerable bulk. Finally, the presence of a substantial population of hypoxic cells also renders tumors less radio-responsive[22,23].

Problems related to a large tumor do not pertain to preoperative irradiation. In this setting, the aim of radiotherapy is to sterilize small cell burdens in the deep infiltrating parts of the tumor as well as micro-extensions into the paravesical tissue and pelvic lymphatics. Such foci might be expected to have a better radiation response because they are better oxygenated. Motivated by these biological factors and by the fact that most of the treatment failures after radical cystectomy for squamous tumors or tumors arising in the bilharzial bladder are caused by local recurrences, preoperative radiation regimens have been implemented in a number of Egyptian centers. A prospective randomized study was carried out at the department of urology, University of Mansoura. The first phase of the study (1976-1979) randomized patients to receive radical cystectomy or 20 Gy preoperative radiation followed by radical cystectomy. The short course, high-dose regimen was selected in view of its logistic simplicity. The 5-year survival for the cystectomy group was 32% and for the radiation plus cystectomy group 39%[4]. The survival data were further correlated to include

the P category and grade of the tumors. Low-stage tumors, irrespective of grade, appeared to be uninfluenced by preoperative irradiation. Patients with high-stage tumors derived a clear therapeutic benefit (20% 5-year survival with cystectomy only vs. 45% in patients receiving preoperative radiation)[21].

Regarding postoperative radiotherapy, the reason for its unpopularity is the widespread belief that intestinal radiation reaction is a major dose-limiting factor due to the fact that large loops of small intestine and colon are exposed to radiation in the irradiation field, since more space becomes available for accommodation within the pelvis. Moreover, adhesions that can develop may fix these loops and tend to expose the same gut segment throughout most of the course of treatment[24].

The rationale for using hyper-fractionation in the present study is the radiobiological hypothesis of an increased therapeutic ratio between tumor and normal tissue when the dose per fraction is reduced. A decreasing fraction size has been investigated in one prospective randomized trial evaluating hyper-fractionation with 1 Gy three times daily to a total dose of 84 Gy compared to the conventional treatment of 2 Gy once/day to 64 Gy in 168 patients unsuited for cystectomy[25]. Both treatments included 2 weeks rest in the middle of the treatment period. The 5 and 10-year survival rates were significantly increased in the hyperfractionation groups. This was confirmed in a Cox multivariate analysis identifying fractionation and stage as independent factors for survival with a hazard rate of hyperfractionation of 1.52[26]. A meta-analysis including studies in all tumor sites has confirmed the effectiveness of hyper-fractionation[27].

In addition to the above radiobiological prediction, the advantage of the potential benefit of attaining more tumor regression after preoperative accelerated hyper-fractionated radiotherapy is that a strong correlation could be demonstrated between the degree of tumor volume reduction after a dose of 40 Gy and the probability of local control at the end of treatment (radical radiotherapy) as well as after 2-4 years[28]. Moreover, a meta-analysis performed on the randomized studies on hyper-fractionation versus conventional fractionation since 1980 has proved superiority of HF over CF in reducing the odds of deaths among patients with bladder cancer[27]. Another advantage for the shortening of the overall preoperative period (6 weeks instead of 8-10 weeks in the other schedules with a similar dose) is a tendency on the part of the patient and the surgeons to avoid a delay of surgery incurred by radiation therapy.

In the present study, the overall 2-year disease-free survival for the whole group of patients was 63.9%, with an overall treatment failure rate of 28.6% (8 patients), and a metastasis rate of 14.3% (4 patients). Pathological staging (P) was used for statistical analysis rather than clinical staging (T), since the "P" category is more accurate, and so, the clinical assessment of the response of the tumor to irradiation was done using CT scan rather than downstaging. The only two prognostic parameters showing significant impact on survival were lymph node infiltration (only when the Cox model was used) and the pathological staging. The impact of other factors did not reach a significant importance, since the number of patients was small. The predictive factors that showed a significant impact on survival in this study (the pathological stage and lymph node infiltration), indicate that treatment of earlier tumors can improve survival.

Soloway et al.[29] reviewed their experience with 130 patients who underwent radical cystectomy for urothelial carcinoma of the bladder and found the pathological stage and lymph node status to be the most important prognostic indicators. Patients with extravesical involvement had significantly worse survival rates compared to those who had organ-confined cancer regardless of their lymph node status.

Cheng et al.[30], in their study on 218 patients treated with radical cystectomy for urothelial carcinoma, reported that tumor size, margin status, T classification and lymph node status were independently predictive of survival.

Minimal acute radiation and no late toxicity were observed among patients of our study. The only two patients who developed severe dysuria requiring interruption of the radiation course had presented with frequent dysuria prior to the initiation of radiotherapy and were bilharzial patients, so they were excluded from the study. There was neither an increased operative difficulty related to irradiation, nor an increased postoperative morbidity.

Pollack el al.[31], in their study on 338 patients with muscle-invasive bladder carcinoma who received preoperative radiotherapy (50 Gy in 25 fractions) followed by radical cystectomy 4-6 weeks later, reported late complications in 3 patients with grade-4 or higher. Two patients experienced rectal complications that resulted in colostomies, and one patient had a small intestinal obstruction. Of those who underwent cystectomy (n= 301), 10 died within 2 months of surgery without evidence of disease. Thus, peri-operative mortality was low.

This work represents a preliminary study illustrating the potential benefits of a new neoadjuvant radiotherapy protocol that might help in improving the survival rate of these patients, especially those with advanced disease. Because the follow-up in this study is not long enough to evaluate patients with bladder cancer, the potential biological advantage of this preoperative radiation schedule aiming at more tumor regression and less late normal tissue reaction, with its impact on disease free survival, remains to be further investigated with a larger patient number and a longer follow-up period.

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Editorial Comment:

Although the study is prospective, unfortunately, it is not controlled. It is difficult to reach a conclusion without a comparison of the proposed protocol of treatment with the standard treatment of radical cystectomy alone and the results of the present study should be compared with a historical group of similar patients who were subjected to radical cystectomy alone.

The authors stated that the preoperative clinical stages of their patients included those with stages T2-T4. It is well known that radical cystectomy is not indicated for T4 tumors. This may explain why 6 patients had inoperable disease on exploration.

Finally, the authors showed that the response to preoperative radiotherapy had no significant impact upon survival in both uni- and multivariate analysis. This could be explained by the observation that the median duration of follow-up was 26 months only which is a very short duration to demonstrate any survival advantage of one category of patients versus others. Also, a 2-year actuarial survival is not sufficient to evaluate patients with bladder cancer.

Reply of the Authors:

We did not include a control group of patients treated by cystectomy alone without irradiation because the survival rates of such patients have been studied before and are well known. The published results showed that the 5-year survival rates of patients with muscle invasive disease were 65-82% for stage T2 and 37-61% for stage T3. In cases with lymph node infiltration, the rate went down to 30%.

We agree that T4 is not an indicated stage for radical cystectomy. Still we included patients with stages T2-T4, because we tried to study the effect of preoperative irradiation on the surgical field and whether it will render an inoperable field operable. During the surgical procedures, six patients were found to be inoperable on exploration and this was probably due to an extensive extravesical infiltration that did not respond to the hyperfractionated doses of irradiation.

This work represents a preliminary study on the potential benefits of a new neo-adjuvant radiotherapy protocol that might help in improving the survival rate, especially in patients with advanced disease. We agree that the follow-up in this study is not long enough to evaluate patients with bladder cancer, and the potential biological advantage of this preoperative radiation schedule aiming at an increased tumor regression and a decrease of late normal tissue reaction remains to be further investigated with a larger number of patients and a longer follow-up period.

RESUME

La Radiothérapie Néo-Adjuvante dans le Carcinome de la Vessie en Egypte
Etude Préliminaire de 56 Patients

Objectifs Evaluer l'impact de la radiothérapie pré-opératoire fractionnée par accélérateurs dans la prise en charge du carcinome vésical chez les patients égyptiens. **Patients et Méthodes** De décembre 1996 à février 2000, 104 patients égyptiens présentant un carcinome infiltrant de la vessie histologiquement prouvé ont été inclus dans cette étude prospective. Les patients de tous sous-types histologiques, présentant des tumeurs non métastatiques, aux stades cliniques T2-T4 et médicalement opérables ont été éligibles pour cette étude. Une dose totale pré-opératoire de 45 Gy a été délivrée en trois semaines à raison de 1,5 Gy/fraction, 2 fractions/jour avec un intervalle de 6 heures entre les séances et 5 fois /semaine. Une cystectomie radicale avec lymphadénectomie a été réalisée trois semaines après la radiothérapie. La réponse clinique de l'irradiation a été évaluée par tomodensitométrie faite juste avant la radiothérapie et reprise juste avant la chirurgie. Seuls 56 patients ont suivi complètement ce protocole thérapeutique. Le délai moyen de suivi était de 26 mois avec des extrêmes de 9 et 32 mois. **Résultats :** La survie actuarielle sans maladie à 2 ans pour les 56 patients était de 63.9 %, dont 50% d'échec due à une récidive pelvienne. L'analyse uni-variée a montré que seule l'envahissement ganglionnaire et le grade histologique étaient significativement corrélés à une survie sans maladie. Il y'avait une amélioration marginale non significative chez les patients qui avaient montré une régression tumorale importante après la radiothérapie. L'analyse multi-variée utilisant le Modèle de Cox a montré que l'envahissement ganglionnaire était le seul facteur prédictif significatif de guérison. Les autres facteurs incluant l'âge, le sexe, le type cellulaire, l'infestation bilharzienne et la réponse clinique à la radiothérapie n'avaient pas d'importance significative quant à la guérison. Une toxicité radique aiguë sans réaction tissulaire tardive a été observée chez tous les patients. Il n'y avait ni majoration de la difficulté opératoire ni de morbidité post-opératoire. **Conclusion** Les avantages biologiques potentiels de ce protocole de radiothérapie pré-opératoire (en terme de raccourcissement de la durée globale du traitement, une dose plus réduite par fraction pour une dose globale équivalente au fractionnement conventionnel), visant à obtenir une réduction tumorale importante et une diminution des réaction tissulaires tardives et son impact sur la guérison nécessitent une évaluation plus approfondie avec un nombre plus important de patients et un suivi plus prolongé.

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