Bone Metastases in Muscle-Invasive Bladder Cancer

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ABSTRACT

Purpose: To address the necessity of incorporating isotopic bone scan in the routine staging work-up of muscle invasive bladder cancer patients, we analyzed the data in our files to determine the incidence of bone metastasis in such patients. The rate of subsequent development of bone metastasis along the natural history of the disease was also investigated.

Patients and Methods: A total of 179 files of consecutive bladder cancer patients who presented to the National Cancer Institute, Cairo University, between January 2000 and December 2001 were reviewed to check the percentage of positive bone scans on presentation and to check the subsequent development of distant metastases and bone metastasis in these patients' records.

Results: Amongst the 179 patients, 26 (14.5%) had bone metastasis on presentation, a finding that showed a statistically significant correlation with the increasing depth of muscle invasion; 61.5% of the metastatic cases had deep muscle invasion, 19.2% had superficial muscle invasion and there was no muscle invasion in 7.7% (p=0.000).

Transitional cell carcinoma was the pathology in 92.3% of those patients, while only 7.7% had squamous cell carcinoma (p=0.036).

The cumulative 3-year incidence of bone-metastasis in the non metastatic patients after treatment mounted to 19.4±4.4%. The cumulative 3-year bone metastasis incidence in the 153 patients was higher with increasing clinical stage; 8.4±8% for c-stage 2 and 49.1±18.5% for c-stage 4 (p=0.046). As for the p-category of the tumor in the 130 patients who underwent operation, the incidence increased with higher p-stages (p=0.006). Though pelvic nodal involvement was not associated with statistically significant increase in the incidence of bone metastases, yet when incorporated as one of the 3 risk factors (grade>3, p≥4a and LN positive at surgery) according to which patients were grouped, there was a statistically significant difference in the incidence between patients with no risk factors, only 1 and 2 or more factors (p=0.021).

Conclusion: Meticulous search for bone metastasis alone or as a component of distant failure in the newly diagnosed bladder cancer patients is crucial to offer them the proper management and avoid undue radical surgical procedures. Thus bone scan is suggested to be performed routinely in patients with evidence of muscle invasion.

Key Words: Bladder cancer - Bone metastasis - Isotopic bone scan.

INTRODUCTION

Identifying the metastatic status is an essential determinant of prognosis in patients with muscle-invasive bladder cancer treated by cystectomy, and preoperative metastases detection is crucial for treatment selection in these patients.

Although the exact rate and pattern of metastases are not well documented, there is a rough estimate that 30% of the patients have undetected distant metastases at the time of treatment of the primary tumor [1].

PATIENTS AND METHODS

A retrospective review was performed of the records of 179 patients with histologically proven bladder cancer who presented to the National Cancer Institute, Cairo University, between January 2000 up till December 2001. Patients who had no initial bone scan on presentation were excluded. Our patients comprised those who underwent radical cystectomy or anterior pelvic exentration with pelvic lymphadenectomy plus urinary diversion, those who were medically unfit for surgery, inoperable, or metastatic at presentation.

The tumors were staged according to the TNM system of the American Joint Committee on Cancer (AJCC) [2]. Positive bone scans at presentation in non-symptomatic patients were
coupled with plain X-rays of the areas of increased uptake in bone scan and in case of a negative X-ray a C.T. or M.R.I. was performed to verify or exclude any bone metastasis. All patients had cystoscopic examination with a biopsy performed to verify the pathological diagnosis, alongside the verification of presence or absence of muscle invasion and its depth. Only 2 pathological reports had no mention of the muscle invasion status.

Statistical analysis:

Comparisons between different percentages and frequencies were performed using the standard Student t-test, F-test, or Pearson’s chi-square test and $p \leq 0.05$ was considered significant. The 3-year cumulative bone metastasis incidences were measured using the Kaplan-Meier product limit method [3]. The period of freedom from distant metastasis or bone metastasis was defined as the period from the date of radical cystectomy or end of radical radiotherapy to the date of occurrence of the first site of distant failure and/or bone metastasis or to the date of evaluation. The log-rank test was used for comparison between survival curves [4].

RESULTS

This is a retrospective analysis of 179 patients with histologically proven urinary bladder carcinoma. The male to female ratio was 3.5:1. Their age ranged from 35 to 82 years, with a mean of 57.4±8.9 and a median of 58.0 years.

The majority of the patients (116 = 64.8%) were clinically stage 3, while 47 (26.3%) were stage 4, and only 16 (8.9%) of them were stage 2.

Twenty six patients (14.5%) had bone metastasis on presentation, 14 (54%) of them were clinically stage 3, 9 (34.6%) were stage 4, while 3 (11.4%) were stage 2 ($p=0.449$).

Looking at the depth of muscle invasion detected histopathologically from the cystoscopic biopsy specimen, 16 (61.5%) of the metastatic cases had deep muscle invasion, 5 (19.2%) had superficial muscle invasion, there was no muscle invasion in 2 (7.7%) cases, while 2 cases had no comment on the muscle invasion ($p=0.000$).

The histopathological subtypes also showed a statistically significant difference concerning the incidence of bone metastasis; 92.3% (24 patients) had transitional cell carcinoma, while only 7.7% (2 patients) had squamous cell carcinoma ($p=0.036$).

Regarding the site distribution of those bony lesions; 8 patients (30.8%) demonstrated a single bone metastasis, while 18 had 2 or more sites (Table 2).

As regards the 153 patients with no metastasis, the cumulative 3-year distant failure incidence amounted to 29.6±4.9%. The 30 patients out of the 153 who experienced distant failure were distributed as follows; 12 patients had isolated bone metastasis (40%), 7 (23%) had bone metastasis plus visceral metastasis (4 lung, 2 lymph nodes, 1 liver), 5 (17%) had only lung metastasis, 3 (10%) had liver while only 2 had isolated supraclavicular lymph nodal metastasis and 1 had intestinal metastasis. Whereas, the cumulative 3-year bone-metastasis incidence was 19.4±4.4% for the same group Fig. (1).

As for the cumulative bone metastasis incidence according to the clinical staging of the
153 patients, the incidence was 8.4±8% for stage 2, 15.4±4.6% & 49.1±18.5% for stage 3 & 4 respectively ($p=0.046$) (Fig. 2). As for the p-category of the tumor in the 130 patients who underwent surgery the incidence was 10±9.5% for p2, 15.8±4.7% for p3, and 53.3±17.1% for p4, these differences were statistically significant at a $p$-value of 0.006 (Fig. 3).

When the incidence was stratified according to the lymph node status (LN) it was 17.9±5.8% for the LN negative cases (66 patients) and 25.4±8.0% for the LN positive cases (64 patients) ($p=0.42$).

The same cumulative incidences were 0% for grade 1, 18.3±5.8% & 25.9±8.5% for grade 2 and 3 respectively, $p=0.39$ (Fig. 4).

On stratifying the patients according to the presence or absence of pathological risk factors, the 3-year cumulative bone metastasis incidence for patients with no risk factors (G<3, $p<4a$ and LN negative at surgery) was 12.9±6.0%. The incidence was 10.2±4.3% for patients who had only one of those risk factors, while the incidence went up to 48.2±13.6% for patients with more than one risk factor. These differences were statistically significant ($p=0.021$) (Fig. 5).
DISCUSSION

There is no consistent data or any systematic review addressing the rate of bone metastasis in newly diagnosed bladder cancer cases. Rather, all published data looked at the rate of distant failure along the natural history of the disease, whether in a retrospective analysis or more so as part of autopsy studies that would thus be assessing metastases at the end point of those cases. Yet dating since 1979 there has been a theory suggesting that bladder cancer may be a systemic disease from the start, where 30% of the study group developed distant metastasis mainly to the lungs and bones- where 80% of them were detected within 1 year from cystectomy suggesting that the metastases must have been present at cystectomy or as a result of it [1]. On the other hand, the more acceptable explanation is that most cancer cells spread by embolization through lymphatics and blood vessels, a theory supported by the identification of 9 patients with superficial papillary tumors with no evidence of muscle invasion in whom distant metastases developed; 5 cases had bone metastases, lung in 3 and liver in 1 [5]. Two out of the 26 patients who presented with bone metastasis at presentation in our study (7.7%) had no muscle invasion at TUR.

When reviewing one autopsy series of untreated patients, the incidence of distant metastases was 65% [6]. Another autopsy study on 367 patients with muscle invasive tumors (pT2-4) found bone metastases in 32% of the cases (ranking third after liver and lung metastases) and the frequency of distant metastases increased with local tumor extension; and was slightly higher in patients treated by cystectomy.
(metastases in 45% if pT2 and 89% if pT4 tumors) than in patients without cystectomy (36% of pT2 and 79% of pT4 tumors) implying that metastasis often occurs before the time of diagnosis [7].

A retrospective study of 145 muscle invasive bladder patients reported distant metastasis as the only site of failure in 23.4% of the cases and associated with local recurrence in 13.1% of the cases [8].

Our results showed a 29.6±4.9% 3-year cumulative incidence of distant failure, 63% of which were detected in bone, thus being in concordance with the study of distant metastasis in bilharzial bladder cancer which reported a rate of 23%. 70% of these distant failures were detected in bone, mainly the pelvis and the spine [9].

Bone metastases were radiographically diagnosed in 24/86 (28%) patients via bone scan and/or bone surveys. Again, the spine and pelvic bones were the most common sites involved. Bony metastases ranked second in frequency after lung metastases [10]. The pelvic bone and spine represented the more frequent sites affected in the skeleton in the present study. They were 32% and 20% respectively (Table 2). Similar results were reported by Sengelov et al. [11].

The incidence of bone metastases upon first presentation was found to be 14.5% of our study group, that was much higher than the data published. The only retrospective study looking at patients with recurrent or metastatic urothelial cancer detected a 4% incidence of metastases diagnosed concurrently with the primary tumor. Whereas bone metastases was the most frequent site of distant metastases occurring in 35% of the cases post treatment, most cases being in the spine and pelvis [11]. However it is worth mentioning that most of the patients in the study of Sengelov et al., were in the superficial bladder cancer category with no muscle invasion. Pelvic bones followed by the spine were also our most frequent anatomical sites involved (52% of cases). An important finding in our study identified the depth of muscle invasion as having a statistically significant effect on the rate of bone metastasis on presentation (p=0.000), which we can only compare to data from other studies yet related to post treatment distant failure [7].

In our present study, patients with transitional cell carcinoma had a statistically significant (p=0.036) higher incidence of bone metastasis on presentation than those with squamous cell. On the other hand, Zaghoul’s study found that squamous cell carcinoma had a 5-year cumulative distant metastasis rate of 15% (CI 13-17%), which was lower than the incidence in transitional cell carcinoma being 39% (CI 33-45%). This difference was statistically significant in univariate analysis. Upon multivariate analysis, he found that this effect was not an independent prognostic factor and it was dependent upon other factors (tumor stage, grade and nodal involvement) [9].

Looking at the pathological prognostic factors affecting the incidence of bone metastasis after treatment, we identified the higher clinical stage (p=0.046), higher pathological tumor stage (p=0.006) and more than one pathological risk factor (p=0.021) as having statistically significant higher incidence of bone metastasis during the course of follow-up of our cases. This is similar to the findings of Zaghoulís retrospective study that identified 3 risk factors on multivariate analysis of 357 patients who were treated with cystectomy alone or in addition to preoperative or postoperative irradiation. The 3 independent risk factors that significantly affected distant metastasis were pathologic stage (p=0.04), histopathologic grade (p=0.05) and pelvic nodal involvement (p=0.005). The author grouped the patients into 3 risk groups; those who had no risk factors (G<3, p<4a and LN negative at surgery), those with only one risk factor and those with 2 or more. The 5-year distant metastases rates were 11±3%, 29±4% and 51±5% for the 3 risk groups, respectively [9]. Applying the same grouping to the patients in the present study revealed also a statistically significant difference between the three groups (p=0.021).

Conclusion:

Bone metastasis as a component of distant failure is rather a substantial element. Having the same importance is the accurate and systematic detection of bone metastasis in the newly diagnosed cases, where a bone scan should be performed to identify such metastasis in cases who prove to have muscle invasion on TUR, or advanced clinical stage, to offer such patients the proper management and avoid undue radical
surgical procedures with all its negative effects on the quality of life of the patient plus an unjustified financial burden. Isotopic bone scan is still an excellent tool to detect bone metastasis during follow up of bladder cancer patients after definitive treatment.

REFERENCES


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