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Original Article

Significance of Grading in Urological Abnormalities in Carcinoma Cervix and its impact on Overall Survival

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ABSTRACT:
Introduction: Cervical cancer is the second most common gynaecological malignancy and notorious for causing urological manifestations in about 20-40% cases. Various abnormalities observed are either due to the local mass effect caused by the disease, from metastatic nodes or due to direct infiltration of urinary bladder. **Materials &Methods:** A retrospective analysis was made of cervical carcinoma cases that were staged and graded on the basis of urological abnormalities using different imaging modalities. An inherent grading system was used to evaluate the urological abnormalities. Outcome was determined in terms of overall survival and quality of life benefits. **Results:** Out of 381 patients enrolled in the study, 284(74.5%) patients were grade 0 followed by 35(9.1%) patients who were grade II. Patients suffering from grade II and III urological abnormalities were offered surgical intervention, however, only 27(50%) patients could undergo surgery due to either medical or monitory reasons. The most common urological intervention done were stenting (unilateral or bilateral) in 18(3.4%) patients followed by percutanous nephrostomy (PCN unilateral or bilateral) in 7(12.9%) patients and only 2 patients underwent radical procedures like anterior resection and illeal conduit. The majority of interventions 17(62.9%) were done in grade II patients. External beam radiotherapy with pelvic field and extended field followed by ICRA was given wherever indicated. All patients were followed for a period of 18 months. Reversal of urological abnormalities was seen in 7% patients, and all of them were in grade II category. On scrutinizing, the majority of grade II abnormalities 30(63.8%) were observed in stage II disease patients. At the end of 18 months follow up, 60.6% patients of grade 0 disease and 68.6% patients in grade I were disease free, whereas (70%) patients of grade II and (21.2%) patients in grade III were disease free at the end of follow up. **Conclusion:** Grading of urological abnormalities serves as a useful prognostic tool to determine the outcome in carcinoma cervix. However, it is imperative that the cases with reversible hydronephrosis should be identified at an early stage and intervention should be done at an early step. Reversible hydronephrosis during treatment is a significant prognostic factor associated with good performance status and better outcome in terms of overall survival.
Key words: Carcinoma cervix, urological abnormalities, grading, prognosis.

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INTRODUCTION:

Cervical cancer is the second most common gynaecological malignancy with an incidence of one lakh women per year with highest incidence noted in less developed countries.[1] Cervical cancer is the second most common cancer in the developing countries with incidence in India being 32 cases per 100,000 women.[3] The primary cause in development of cervical cancer is human papilloma virus (HPV). More than 90% of squamous cell cancers of cervix contain HPVDNA.[2] Over 70% of the cases present in advanced stages with poor prognosis and high mortality rates.[4]This may be attributed to high rates of illiteracy and poor hygiene. There are two criterias for the diagnosis of stage IIIB cervical cancer in the FIGO staging system: tumor fixation to the pelvic side wall and/or the presence of hydronephrosis due to tumor. However the treatment may be difficult due to presence of uremia due to obstructive uropathy. This is due to either external compression or malignant involvement of lower ureters. However, we often encounter hydronephrosis without tumor fixed to the pelvic side wall or the level of ureteral obstruction not corresponding to the main tumor mass in the pelvis. The clinical implication of these phenomena remains unclear. The study at Mallinckrodt Institute of Radiology

concluded that additional presence of hydronephrosis did not significantly worsen the progression free survival (PFS) among stage IIIB patients with tumor fixation to the pelvic side wall. However, hydronephrosis without tumor extending to the pelvic side wall or the level of ureteral obstruction above the true pelvis was associated with poor outcome due to a significant increase in distant failure.[5] Hydrouretero nephrosis is the most common feature observed on imaging modalities in advanced cases of carcinoma cervix. It often guides as an implementary tool in selected patients. Very frequently, it is difficult to offer adjuvant management in view of co-existing uraemia due to obstructive uropathy. This is due to either external compression due to para-aortic lymph nodes or treatment refractory progressive disease. Uremia occurring secondary to obstructive uropathy is a common cause of death in cancer of cervix. Urinary diversion by percutaneous nephrostomy (PCN) is the most commonly practiced urological intervention, not only to improve renal function (6massry) but also to improve quality of life and enable the patient to accept tumor specific palliative treatment in most cases and curative treatment in some cases.

MATERIALS & METHODS:

This is a ten years retrospective study which included all patients with biopsy proven carcinoma cervix, treated in Department of Radiotherapy at Christian Medical College & Hospital, Ludhiana. All cases were staged and graded on the basis of urological abnormalities using imaging modalities i.e. intravenous pyelogram (IVP) and contrast enhanced tomograms (CECT). All patients underwent clinical examination before investigation. The various urological abnormalities were graded as per the following criteria.

Grade 0: No deviation of ureters or renal functional impairment.

Grade 1: Anatomical deviation of ureters.

Grade 2: Unilateral or bilateral hydroureter or hydronephrosis (HDN).

Grade 3: Delayed or non functional kidney on IVP with deranged renal parameters.

Results: Out of 381 patients enrolled in the study, the most common stage identified was stage III with 180 (47.2%) patients, followed by stage II with 120 (31.4%) patients, stage I with 46 (12.07%) and stage IV with 35(9.1%) patients. All patients underwent imaging using either intravenous pyelograms (IVP) or computerized tomography (CECT). On the basis of imaging and renal functions, a total of 284 (74.5%) patients were grade 0, 35(9.1%) patients were grade I, 47(11.2%) patients were grade II, and 7(1.8%) patients were grade III. In grade 0 and grade I, no intervention was done. Patients suffering from grade II and III urological abnormalities were offered surgical intervention, however, only 27(50%) patients could undergo surgery due to either medical or monitory reasons. The most common urological intervention done were stenting (unilateral or bilateral) in 18(66.6%) patients followed by percutanous nephrostomy (PCN unilateral or bilateral) in 7(25.9%) patients and only 2 (7.4%) patients underwent radical procedures like anterior resection and illeal conduit. The need for PCN insertion was judged by ultrasound findings of hydronephrosis with obstruction of pelvic ureters, associated with high serum creatinine and BUN levels. The majority of interventions 17(62.9%) were done in grade II patients. Following initial management all the cases were treated by concurrent chemo-radiotherapy or radiotherapy alone, depending on the renal function status of the patient. Radiotherapy was given by either pelvic field or by extended field depending upon the extent of the disease, followed by intracavitary radiation application (ICRA).

All patients were followed for a period of 18 months. During the initial 12 months of follow up reversal of urological abnormalities was seen in 7% patients, and all of them were in grade II category. On scrutinizing, almost all of them belonged to stage II. At the end of 18 months follow up, 60.6% patients of grade 0 disease and 68.6% patients in grade I were disease free, whereas (70%) patients of grade II and (21.2%) patients in grade III were disease free at the end of follow up.

TABLE 1: Distribution of patients correlating the grade and stage of presentation

	GR 0	GR I	GR II	GR III
STAGE I (19)	19	0	0	0
STAGE II (96)	80	16	0	0
STAGE III (228)	100	78	30	10
STAGE IV (38)	4	20	7	7
TOTAL (381)	203	114	37	17

TABLE 2: Distribution of patients undergoing urological intervention according to stage

	STAGE II	STAGE III	STAGE III
STENTING	9	6	1
PCN	3	5	1
URINARY DIVERSION	-	-	2
TOTAL	12	11	4

TABLE 3: Distribution of patients according to grading of urological abnormalities and the intervention

GRADE	STENTING	PCN	OTHERS
0	-	-	-
I	-	-	-
II	13	4	-
III	5	3	2

TABLE 4: Distribution of patients correlating the grade of urological abnormalities and the disease free survival at six monthly follow-up

GRADE	0-6M	7-12M	13-18M
0	80.34%	60.56%	60.6%
I	89.8%	72.6%	68.6%
II	87.8%	75%	70%
III	76%	35%	21.2%

DISCUSSION:

Discussion Cervical cancer is a preventable disease. Early diagnosis and effective treatment is possible, thanks to various screening strategies (Demirtas, 2013). Primary intention should be prevention or early diagnosis, and screening programs constitute be the main focus. It is well known that the incidence of cervical cancer increases with age (Nartthanarung et al., 2014). Likewise in our study the incidence of cervical cancer along with urological abnormalities was the highest in 51-60 years age-group %. Pelvic sidewall involvement is not always associated with hydronephrosis. Disease stage is the most important prognostic variable in cervical cancer. The more advanced cancer is the lesser the overall survival. Likewise, our present study also the most demonstrated that hydronephrosis was associated with less survival. Likewise, our present study also demonstrated that hydronephrosis was associated with less survival. However, we did not observe a significant survival difference between patients with unilateral and bilateral hydronephrosis. As a result, it was concluded that hydronephrosis had unfavorable effects on survival, irrespective of laterality. Among the patients with stage IIIB tumors, although the stage is not altered in the presence of hydronephrosis, survival is significantly shortened, nearly approaching survival durations of patients with stage IV disease. In light of these findings, we recommend that stage IIIB tumors should further be stratified into subgroups according to presence of hydronephrosis. Hydronephrosis was first reported by Michael Hopkins to have prognostic value in stage IIIB cervical cancer. In his study, five years survival rate in patients with normal IVP with no obstruction was 47% with uretric obstruction without renal failure was 29%. Contrary to this all patients with uretric obstruction with renal failure died within 16months.[7] whereas in our study only 21.2% patients with moderate to severe uretric obstruction (grade III urological abnormality) were disease free at the end of 18 months follow-up. Another well attempted study was done by Pradhan et al[8], where hydronephrosis was studied as a prognostic indicator for survival in advanced cervical cancer. In this study it was concluded that hydronephrosis is an independent poor prognostic indicator of survival in patients with advanced cervical cancer. It was also observed that bilateral hydronephrosis compared to unilateral involvement confers a worse overall prognosis.[8] Our study also fared the same outcome with bilateral hydronephrosis conferring poor overall survival. However, in order to substantiate the results of our study, additional randomized multicentric trials are needed to determine if FIGO staging should be amended regarding unilateral and bilateral hydronephrosis and its impact on overall survival. In a study by Rose et al, in which impact of hydronephrosis was studied on the outcome of stage IIIB cervical cancer patients with disease limited to the pelvis, treated with radiation and concurrent chemotherapy, it was observed that patients with stage IIIB cervical cancer restricted to the pelvis, hydronephrosis at presentation is a significant but not independent prognostic factor associated with poor performance status and poorer survival and relief of ureteral obstruction is correlated with improved outcome.[9] Along with hydronephrosis other prognostic factors having clinical impact on disease specific survival are bilateral pelvic wall involvement, clinical tumor diameter ≥ 8cms; lower vaginal involvement and evidence of lymph node metastases on lymphangiogram were seen.

Percutaneous nephrostomy was first described by Goodwin et al in 1955.[7] The most important factors determining extent of recovery of renal function are extent of duration and obstruction.[10,11] In our study most of the patients who presented in grade II or III categories were long standing cases. A complete history including onset of the first symptom and its persisting duration confirmed our findings. In grade II category 18.1% patients underwent PCN whether unilateral or bilateral and 54.5% patients underwent stenting. In grade III 30% underwent PCN and 1 patient had stenting. PCN is especially useful in obstructive uropathy due to irreversible cause in cervical cancer, since retrograde uretric stenting is often not possible. The low failure rates in our study reflect that although it is an invasive procedure, it is very simple and feasible. The only contraindication is bleeding diasthesis. Hyppolite Jean-Claude[12] in his study of obstructive uropathy in gynecological malignancies found

bilateral nephrostomy to be superior to unilateral nephrostomy and even to intraureteric stenting. One of the most important advantages of PCN was that we could administer tumor specific treatment in 83% i.e. curative radiotherapy in three and palliative radiotherapy or chemotherapy in seven out of 12 untreated patients. Decision to do invasive PCN should be individualized in cervical cancer patients presenting with deranged renal functions as a result of obstructive uropathy, on the basis of availability of subsequent definitive treatment options. In previously treated patients with no recurrence, role of PCN as an emergency temporary measure to avoid renal failure is unquestionable. In carefully selected patients, primarily with advanced disease it improves quality of life and prolongs survival by enabling tumor specific treatment. It increases acceptability to palliative radiotherapy or chemotherapy by correcting deranged renal functions. In small but definite number of cases, even curative treatment with long survival could be achieved. However, its role in recurrent or residual disease (where no further tumor directed treatment is available) seems controversial.

Obstructive uropathy with uremia with the risk of impending irreversible damage is a common presentation in a significant proportion of cervical cancer patients in developing countries. Decision regarding invasive procedures should be individualized in cervical cancer patients presenting with deranged renal functions due to obstructive uropathy, on the basis of stage of the disease, overall prognosis and availability of subsequent definitive treatment options. In previously treated patients with no recurrence, role of urological intervention as an emergency temporary measure to avoid renal failure is unquestionable.

In selected patients who present primarily with advanced disease it improves quality of life and prolongs survival by enabling treatment. However, its role in recurrent or residual disease seems controversial. It is because uraemic death is much sweeter than death due to fistula or severe neuropathic pains, where we have very limited options available. Thus, decision making process is complex. Counseling is essential and the wishes of the patient and her family have to be considered. Important factors to be taken into consideration before any urological intervention, may be extent of disease and its status in terms of primary or recurrent or residual disease, availability of treatment options, patient performance status and associated medical comorbid conditions. At the same time it is always essential to explain in detail every possibility and unpredictability of results to patients and relatives. Most studies reported in literature are retrospective, small sample based and non-randomised. Therefore, the role of urological intervention in management of obstructive uropathy in cervical cancers actually needs to be defined more accurately in terms of survival benefit or quality of life improvement in large sample based, randomized, prospective trials.

Conclusion: In treated and cured patients with long life expectancy, urological intervention was effective as a temporary means to save renal functions until retrograde stenting/surgical diversion could be offered. In treatment naïve patients, any intervention was effective to improve renal function and allowed definitive treatment in many cases. In many cases, the intervention could be reverted back once the obstruction was relieved by tumor regression. In patients who have recurrence after completing definitive treatment and who presented with uremia, the only benefit of intervention is to prolong life. As no other definitive treatment could be offered after intervention, their role in such cases is controversial. Hence, urological intervention is safe, feasible and should be done in carefully selected cases. It should be avoided in cases where it only serves to prolong suffering. Grading of urological abnormalities in carcinoma cervix can be used as an implementary tool in prognosis and treatment decisions. Presence of hydronephrosis or hydrouretronephrosis is a useful prognostic factor in carcinoma cervix. In grade I and grade II disease aggressive urological intervention may lead to complete recovery and effective treatment outcome of the patients. In later grade III and IV it is advised to judicially select any type of urological intervention in the patients who might benefit from it rather than prolonging the suffering and agony. Last but not the least the wish of the patient should be of prime importance.

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