

Cervical cancer: Renal complications and survival after percutaneous nephrostomy

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SUMMARY

Introduction: Obstructive nephropathy is a frequent complication in the course of advanced cervical cancer (CC), and ultrasonography-guided percutaneous nephrostomy (PCN) is a well established technique for fast ureteral desobstruction.

Objective: To identify possible factors related to the survival and quality of life of patients with advanced CC presenting acute urinary obstructive complications that after desobstruction by PCN recovered urinary flux and renal function.

Method: This is an analytical, descriptive, cross-sectional study that included 45 patients with CC who underwent PCN and were divided into 2 groups: “death” (DG) and “survival” (SG), in a public hospital that is reference for oncologic diseases in Northern Brazil.

Results: The mean serum creatinine of the patients preceding PCN was >10 mg/dL, and after PCN <2 mg/dL. The cutoffs of 8.7 g/dL for Hb ($p=0.0241$) and 27% for Ht ($p=0.0065$) indicated the values that better discriminate the outcomes of the groups. The presence of low blood pressure was statistically correlated ($p=0.0037$) to the outcome “death”. Changes in glomerular filtration rate (already reduced in all cases) were not associated to the levels of Hb/Ht or to the outcome “death” during the nephrological follow-up.

Conclusion: PCN was responsible for the recovery of renal function in 61.7% of the patients, leading to interruption of renal replacement therapy (RRT) in all of those patients. Hb levels >8.7g/dL and Ht >27% were associated to longer survival, and the presence of low blood pressure during follow-up was associated with progression to death.

Keywords: ureteral obstruction, chronic kidney injury, percutaneous nephrostomy, anemia, creatinine, survival.

Study conducted at Hospital Ophir Loyola, Belém, PA; and at Universidade Federal de São Paulo (Unifesp), São Paulo, SP Brazil

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INTRODUCTION

Cervical cancer (CC) is one of the most common cancers in women, especially in developing countries, constituting a real public health problem.¹

Prevention of CC is potentially effective, as there are various forms of intervention and combating the multiple manifestations of the disease. However, despite the effectiveness of control programs in many centers, CC remains a disease with high prevalence, incidence and mortality.²

Despite advancements in the treatment of urogenital neoplasms, surgical techniques, radiotherapy and chemotherapy, we still observe the frequent progression to

obstructive urinary complications due to local expansion or pelvic metastases,³ which characterizes CC as the main pelvic tumor progressing with urinary obstruction.⁴

The development of obstructive acute renal failure (ARF) in patients with a malignant neoplasm results in an ethical dilemma, as renal clearance may often only be accomplished through invasive palliative procedures such as percutaneous nephrostomy (PCN), which in some cases may compromise quality of life.⁵

Note that in advanced stages of neoplastic disease treatment is always challenging, and thus interventions should prioritize the patient’s quality of life, pain relief, assurance of hygiene and psychological care.^{6,7}

Considering the high mortality found among patients with advanced CC, particularly if complicated by obstructive ARF, studies are needed to evaluate the factors that may influence the survival and quality of life of such patients. The identification of such factors after renal clearance was the main goal of the present study.

METHOD

This is a descriptive, analytical cross-sectional study involving patients with advanced CC. The study was conducted at Hospital Ophir Loyola (HOL), which is a reference center in care and tertiary level treatment of cancer cases in the Northern part of Brazil. The project was submitted to the Ethics and Research Committee at the Universidade Federal de São Paulo, and approved.

Initially, the medical records of 963 patients admitted to the hospital due to a diagnosis of ARF were assessed by the Nephrology Team. The analysis period lasted from January 2010 to June 2012. We selected ninety-nine medical records of patients with CC who were submitted to PCN after being diagnosed with stage 3 (dialytic) ARF⁸ according to the AKIN-KDIGO classification. Sixty-one of them were discharged with improvement; 16 remained on dialysis or died; and the 45 remaining patients returned for monitoring, constituting the study group presented here (Figure 1).

We analyzed the 45 selected patients at two different times: at admission (diagnostic and therapeutic interventions including the outcomes), and in the outpatient clinic (therapeutic and diagnostic interventions, monitoring and complications). The inclusion criteria used were: female gender, being admitted to the hospital (HOL) with a diagnosis of CC (stages IIIB and IV), being over the age of 18 years, having a clinical, radiological and laboratory diagnosis of bilateral ureteral urinary obstruction, having been submitted to renal replacement therapy (RRT), and having presented recovery of kidney function after PCN.

It is worth mentioning that after PCN all 45 patients recovered renal function and were discharged from the hospital and referred to outpatient monitoring with the Urology and Nephrology teams.

We excluded those patients who did not recover kidney function and continued on RRT, those that progressed to death before discharge, and those presenting urinary obstruction due to gynecologic etiologies other than CC.

The 45 patients who participated in the study were divided into two groups: DG (deceased group – formed by patients who had died by the time the data was collected) and SG (survival group – patients who were still under outpatient monitoring).

The assessment of the ARF symptoms was limited to analyzing the recovery of renal function through: restoration of urinary flow and a decrease in serum levels of urea and creatinine by at least 50% of its value upon diagnosis of ARF.

The stages of chronic kidney disease (CKD) were based on the estimated glomerular filtration rate (GFR) by the equation of the “Modification of Diet in Renal Disease” (MDRD).⁹

Treatment evaluation and tumor staging were based on medical notes and complementary examinations (the International Federation of Gynecology and Obstetrics staging criteria).¹⁰

In the evaluation of in-hospital mortality as well as after discharge the simple frequency of death was used.

After discharge, the results of laboratory tests at two times during outpatient monitoring were compared: 1) first sample relating to the initial evaluation by the teams after discharge, and 2) final sample for the last visit noted in the medical records in both groups (at the time of collection).

The following statistical tests were used for data analysis: Student’s t-test, Mann-Whitney U test, Fisher’s exact test and Chi-square test, logistic regression and ROC curve.

RESULTS

We initially evaluated 963 external care forms from the Nephrology sector, selecting 293 (30.4%) that belonged to patients with CC and ARF.

Dialytic post-renal AKIN 3 was found in 144 cases (49.4%), with PCN being used as the clearance treatment in 99 (68.7%). Among the patients submitted to PCN, we noted 61 cases (61.7%) of recovery of kidney function, 25% resulting in in-hospital death and 13% remaining on RRT. Only 45 (73.7%) of patients submitted to PCN returned to outpatient monitoring and the remaining 26.3% never returned (Figure 1).

All 45 patients constituting the object of the research were initially cared for by the Nephrology team in dialytic emergency, and submitted to RRT and PCN, the urological procedure for renal/ureteral drainage and clearance, progressing with recovery of renal function and discharge from RRT.

The selected patients were evaluated on the basis of two types of outcomes: survival group (SG, n=13) and death group (DG, n=32, Figure 1). The 45 patients were female, with an average age of 53.1±12.4 years in SG and 46.2±14.6 years in DG (p=0.1409).

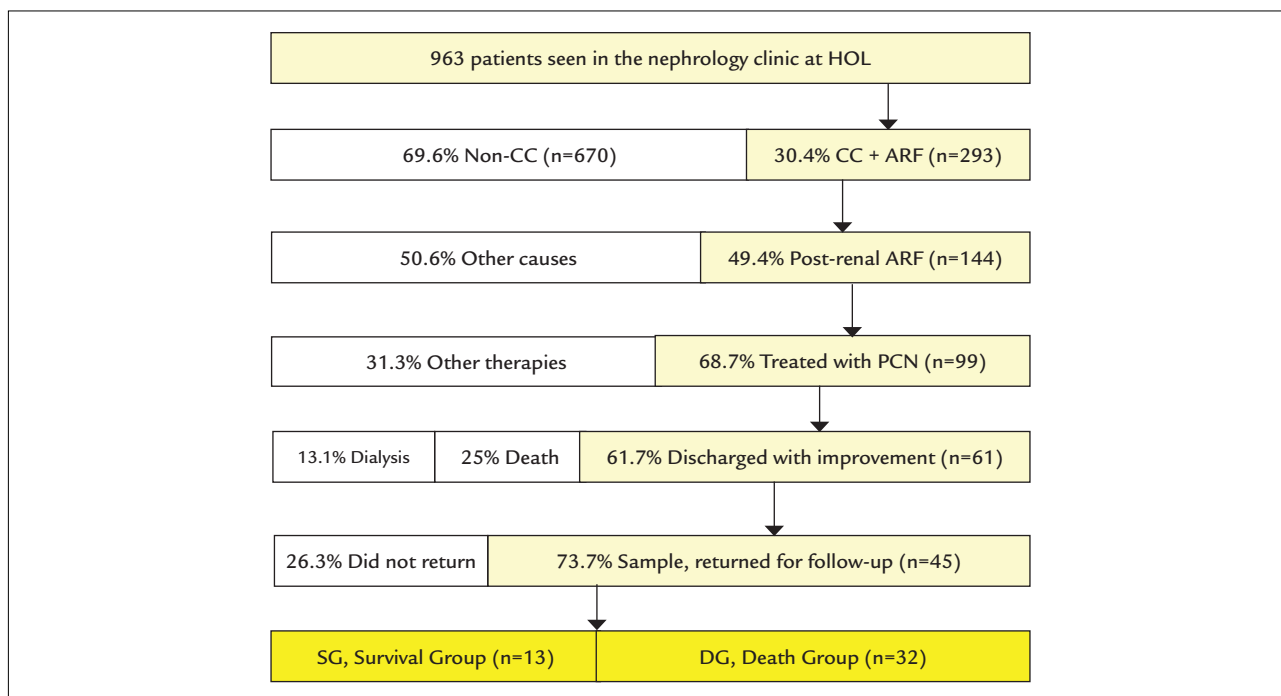


FIGURE 1 Selection of the 45 patients who participated in this study and the evolution of cases of urinary obstruction secondary to CC after nephrostomy.

HOL: Hospital Ophir Loyola; CC: cervical cancer; PCN: percutaneous nephrostomy; ARF: acute renal failure.

In ARF assessment, the groups did not differ statistically in regard to serum levels of creatinine ($p=0.5605$) and urea ($p=0.5256$), dialysis time ($p=0.6530$) and nephrostomy time ($p=0.5256$). The initial laboratory characterization of ARF showed: 11.5 mg/dL of creatinine and 188.7 mg/dL of urea in SG and 10.1 mg/dL of creatinine and 165.4 mg/dL of urea in DG. The average dialysis time before the PCN was 22.6 days in SG and 25.3 days in DG. The average nephrostomy time was 6.6 months in SG and 7.6 months in DG (Table 1).

Comparing the results obtained in relation to the clinical characteristics of the neoplastic disease, there was no statistically significant difference ($p>0.05$) between groups: current situation of tumor treatment in ARF care ($p=0.2912$) and neoplastic clinical staging ($p=0.9074$). As to the type of treatment conducted, the groups showed no significant difference: radiation therapy ($p=0.8605$), chemotherapy ($p=0.2019$) and surgery ($p=0.7422$). Most patients were submitted to radiation therapy (SG 92.3% and DG 93.8%). In SG, chemotherapy was given to 30.8% and surgical treatment to 23.1% of patients. In DG, chemotherapy was given to 12.5% of patients and surgery to 18.8% (Table 2).

With respect to outpatient monitoring after hospital discharge, the comorbidities did not differ in a statistically significant manner between the groups ($p>0.05$). Note that hypertension (38.5% in SG and 21.9% in DG, $p=0.4422$)

TABLE 1 Lab workup (blood dosages) and progression of the 45 patients with CC according to groups (SG = survival, and DG = death).

Variable		SG	DG	p value
Creatinine in ARF	(mg/dL)	11.5	10.1	0.5605
Baseline creatinine		1.86	1.94	0.4157
Final creatinine		1.75	1.94	0.7353
Urea in ARF	(mg/dL)	188.7	165.1	0.5256
Baseline urea		45.91	52.42	0.0971
Final urea		51.82	68.9	0.2585
Baseline glomerular filtration rate	(mL/min)	47.9	51.8	0.5817
Final glomerular filtration rate		58	54.4	0.7926
Nephrostomy	(months)	6.6	7.6	0.5256
Renal replacement therapy	(days)	22.6	25.3	0.6530
Baseline hemoglobin	(g/dL)	9.27	8.47	0.0641
Final hemoglobin		9.99	8.25	0.0241
Baseline hematocrit	(%)	26.94	24.99	0.2794
Final hematocrit		30.5	23.6	0.0065
Baseline sodium	(mg/dL)	137.2	135.8	0.5278
Final sodium		137.7	133.5	0.087
Baseline potassium	(mEq/L)	4.33	4.23	0.4398
Final potassium		4.56	4.18	0.3675

ARF: acute renal failure.

TABLE 2 Cervical cancer status, treatment and complications during PCN in the survival (SG) and deceased (DG) groups.

Variable	SG (13)	%	DG (32)	%	p-value
Treatment status					0.2912
Naïve	0	0.0	2	6.3	..
Under treatment	5	38.5	16	50.0	..
Recurrent with TP	4	30.8	3	9.4	..
Recurrent without TP	4	30.8	10	31.3	..
Staging					0.9074
III	5	38.5	10	31.3	..
IV	8	61.5	22	68.8	..
Treatment performed					..
Radiotherapy	12	92.3	30	93.8	0.8605
Chemotherapy	4	30.8	4	12.5	0.2019
Surgery	3	23.1	6	18.8	0.7422
Complications					
Gross hematuria	0	0.0	1	3.1	0.4857
Accidental loss of the tube	2	15.4	5	15.6	0.9998
Urinary tract infection	6	46.2	13	40.6	0.7512
Skin infection in the tube's exit orifice	1	7.7	4	12.5	0.9877
Rash in the exit orifice	0	0.0	1	3.1	0.4857
Pain at the tube's insertion site	2	15.4	1	3.1	0.1961
Pyelonephritis	0	0.0	0	0	..
Sepsis	0	0.0	1	3.1	0.4857
Hyperkalemia	3	23.1	3	9.4	0.3342
Low blood pressure	2	15.4	18	56.3	0.0197*

TP: therapeutic possibility; hypothesis tests: Student's t and Mann-Whitney; *Fisher Exact Test.

and deep vein thrombosis (23.1% in SG and 12.5% in DG, $p=0.3942$) were the most frequent comorbidities.

In the evaluation of the laboratory characteristics during monitoring, baseline and final serum creatinine and urea in both groups were not statistically different; however, these findings characterized persistent renal dysfunction in both groups despite clearance of the urinary transit (Table 1).

Among laboratory variables that influenced progression to death, we can highlight the level of hemoglobin (Hb) which, in the final evaluation, differed statistically between SG and DG ($p=0.0241$, Table 1). The cutoff point of 8.7 g/dL of Hb (ROC curve) indicates the value that best discriminates DG and SG, with 83.3% sensitivity, 56.7% specificity and 64.3% accuracy. The test's negative predictive value of 89.4% indicates high reliability in re-

lation to prognosis (survival), when the patient presents $Hb \geq 8.7$ g/dL. On the other hand, the test's positive predictive value of 43.5% indicates high reliability in relation to a prognosis indicating death, when the patient presents $Hb < 8.7$ g/dL.

The final Ht was also statistically different between the groups ($p=0.0065$, Table 1), in which case the Ht value that best discriminates patients depending on the outcome (death *vs.* survival) resulted in a cutoff point of 27.0%, which presented 76.9% sensitivity and 64.5% specificity.

Certain complications were noted in the groups during monitoring. Urinary tract infection showed a high frequency in both groups (46.2% in SG and 40.6% in DG). Hyperkalemia was found in 23.1% of SG and 9.4% of DG in more than two samples collected during monitoring. DG presented a high frequency of low blood pressure (56.3% in DG and 15.4% in SG). This finding differed in a statistically significant manner between the groups ($p=0.0197$, Table 2).

The evaluation of the glomerular filtration rate (GFR)-MDRD at baseline did not statistically significantly differ ($p=0.5817$) in the comparison between SG and DG. The same was also true for final GFR-MDRD ($p=0.7926$). There was no evidence of any relationship between the stage of CKD established by the MDRD equation and Hb levels or the evolution of the groups.

The multivariate logistic regression model identified a variable that was associated in a highly significant manner with death as an outcome, which was the occurrence of hypotension ($p=0.0037$). In this last analysis, the Hb ($p=0.4497$) and Ht ($p=0.4748$) variables were not statistically significant. The low blood pressure variable evaluated using Fisher's exact test ($p=0.0228$), as well as by multivariate analysis, was really associated with the death of the patients as a risk factor, with an odds ratio of 7.8 (95CI between 1.3 and 55.8).

DISCUSSION

Despite the existence of CC control programs in many centers, cervical cancer remains a disease with high prevalence, incidence and mortality. Every year half a million women are affected by this disease worldwide and 50 percent of them die due to CC.²

CC is the third neoplasm in Brazil that affects the female gender, and is more frequent in the Northern region, where it occupies first place among women in the state of Pará (24 cases/100,000).⁷

The incidence of ARF in cancer patients has been described in 27¹¹ to 33%¹² of the cases in different services. Knowing that ARF is an independent predictor of in-hos-

pital death,¹³ the teams caring for patients with CC have united in an effort to change this outcome at the HOL.

Among the palliative treatments available for this group of patients with “malignant” ureteral obstruction due to local invasion, PCN has been used to restore urine flow in cases where anatomical deformities secondary to neoplastic disease and/or the clinical conditions of the patients do not enable other treatments.

We identified that 30.3% (293) of the cases of ARF attended at HOL were related to CC, which shows that a significant portion of the ARF diagnoses are associated with CC at this service. One hundred and forty-four (49.4%) of these cases presented urinary obstruction, which represents 15% of all ARF appointments at the hospital. This finding differs from that reported in the BIRMA Cohort Study (Belgium),¹⁴ which noted a 6.5% incidence of gynecological cancer as a cause of this complication, perhaps reflecting a more effective primary prevention. In a Brazilian study,¹⁵ the authors also found a low incidence of post-renal ARF, which was around 2 to 4%.

PCN was conducted on 99 (68.7%) of the 144 patients with urinary obstruction, while the remainder (45) did not present clinical conditions or refused treatment. After PCN, we noted the following developments: 61.7% were discharged with sufficient recovery of renal function to undergo outpatient monitoring without RRT, similar to the findings of the Romero group, which noted that 60.5% of patients undergoing urinary derivation due to “malignant” ureteral obstruction could return to their homes.³ A significant number of patients submitted to PCN did not regain renal function, remaining on RRT (13%), which is in accordance with findings from an international multi-center study,¹⁶ which found that 13.8% remain on dialysis, while 25% of patients progressed to death during hospitalization. This is a relatively low mortality rate when compared with the findings of Benoit and Depuyd¹⁷ who reported an in-hospital mortality rate of 85% among patients with cancer and ARF undergoing dialysis during hospitalization. In an international study that evaluated 1,738 patients with ARF (dialytic and non-dialytic) admitted to an intensive care unit,¹⁶ the authors reported a 76.8% mortality rate in the sample corresponding to Brazilian patients (n=153). It is important to say that the evaluation of mortality described in this study was limited to simple frequency of death among the 99 patients who were subjected to RRT/PCN.

In relation to the recovery of renal function after clearance by PCN in our study, both groups benefited without distinction from the procedure, moving from serum levels of creatinine of 11.5 (SG) and 10.1 mg/dL (DG) to

1.86 (SG) and 1.94 mg/dL (DG). The same occurred with urea serum levels (Table 1).

Despite the benefits observed after installation of the PCN, in relation to the recovery of urinary flow and the possibility of leaving hospital, the mortality during monitoring after discharge among the 45 patients being accompanied was significantly greater than in-hospital mortality, given that 71% of patients progressed to death (32/45) during outpatient monitoring (Figure 1).

DG patients had a worse survival despite being younger, although this finding did not present statistical significance. This observation is in accordance with the findings of Nakagawa et al., who described lower survival rates in women with CC aged less than 50 years.¹⁸

There was a high frequency of urinary tract infection in both groups (46% in SG and 40.6% in DG). The treatment used the most was oral antibiotics at home. Three percent of the DG patients presented sepsis from urinary infection that might be related to the PCN. Serious complications such as abscesses, sepsis or hematoma associated with the PCN occur in less than 5% of cases.⁵ Hyperkalemia was diagnosed more than twice in 23% of the SG and 9.4% of the DG during monitoring, without any tubular disorders having been identified. It is known that after urinary obstructive conditions, tubular disorders may occur that affect the reabsorption of electrolytes. These changes may occur either in isolation or in conjunction.⁵

Time of use of the PCN after discharge was 7.6 months in the DG and 6.6 months in the SG, which is consistent with the findings of Dagli and Ramchandani, who described survival and permanence of the tube for 6.8 months.¹⁹

Recent studies have indicated the benefits of using PCN in the treatment of urinary obstruction. Advanced malignant neoplasms have been the main indication for PCN, corresponding in different studies to 61,¹⁹ 52²⁰ and 58%.²¹

Analysis of the medical history revealed that high blood pressure (HBP) was the most frequent associated disease in both groups (38% in SG and 21% in DG), differing from the findings of the Ministry of Health, which describes 14% HBP in the general population.²² Perhaps the impairment of renal function that remained chronic in the groups can be related to an increase in the frequency of HBP.

When we analyzed renal dysfunction through the average GFR, we noted that this did not differ between the groups, with 54 mL/min in DG and 58 mL/min in final laboratory evaluation. The reduction in renal function did not influence the evolution of the patients in the survival and deceased groups, and was also not associated with anemia (hemoglobin and hematocrit levels). We used the MDRD

formula to measure the GFR as modified by Bastos,⁹ which only relies on age, sex and serum creatinine, given that during monitoring most patients did not present clinical conditions for the measurement of weight and had reduced muscle mass due to the advanced stage of the disease. Therefore, the GFR found may have been underestimated.

The presence of anemia in cancer patients is a frequent finding, leading to a significant impact on quality of life and survival time and may increase the risk of thrombotic events. These adverse effects are also observed in patients with chronic renal failure without neoplastic disease.²³ Anemia in patients with neoplasm can be explained by several factors such as the increase in the cytokine interferon gamma, tumor necrosis factor alpha, interleukin (IL) IL1, IL6.²⁴ As expected, anemia was a frequent finding in the groups studied, with an average final Hb (last collection) of 9.35 g/dL in SG and 8.3 g/dL in DG, which is a statistically significant difference ($p=0.0241$).

The ROC curve enabled us to identify that the levels of final Hb of 8.7 g/dL ($p=0.0241$) and final Ht of 27% ($p=0.0065$) are the values that best distinguish the evolution of the patients studied, as values above these favor a greater survival rate while lower values favor progression to death. It should be made clear that treatment with human erythropoietin was not used in the groups.

A finding that drew a lot of attention in this study was the occurrence of low blood pressure, which was particularly more common in DG (56% in DG *vs.* 15.4% in SG, $p=0.0197$). It is worth mentioning that this was not associated with symptoms of sepsis, but it is possible that its occurrence, which is associated with a worse prognosis, results from a set of characteristics in these patients, such as anemia, malnutrition, remaining in a reclined position for a long time, dehydration (low circulating volume), frequent use of opioids, etc.

The multivariate analysis showed that among the clinical complications not related to the PCN itself, the presence of hypotension had an important influence on the "death" outcome ($p=0.0037$), but not the Hb ($p=0.4497$) and Ht ($p=0.4748$) variables. Low blood pressure unrelated with septic symptoms appeared as a risk factor for death, with an odds ratio of 7.8 (95CI between 1.3 and 55.8), which is in accordance with the findings of de Silva Júnior et al., who evaluated critically ill patients hospitalized at intensive care units, in which the presence of hypotension was associated with progression to death ($p=0.001$).²⁵

CONCLUSION

By analyzing the clinical and laboratory progression of 45 women with CC treated with PCN due to obstruction

of the urinary tract, we can conclude that PCN allowed the recovery of renal function and hospital discharge in 61.7% of the patients, dispensing with RRT. It is noteworthy that serum creatinine was greater than 10 mg/dL before the procedure and less than 2 mg/dL afterwards. The average time for remaining with the nephrostomy was 6.1 months in SG and 5.3 months in DG (Table 1). The most frequent complication related to the presence of the PCN tube was urinary tract infection. In relation to survival, among the various factors evaluated we can highlight the levels of Hb/Ht and the occurrence of hypotension. Levels of Hb >8.7 g/dL and Ht >27% were associated with greater survival among patients. A variation in the glomerular filtration rate, which was already low in all cases, was not associated with the levels of Hb/Ht or progression to death during nephrological monitoring. The presence of hypotension during monitoring of patients with advanced CC was associated with progression to death and, in general, was not a result of sepsis.

RESUMO

Câncer de colo uterino: complicações renais e sobrevida após nefrostomia percutânea

Introdução: a nefropatia obstrutiva é complicação frequente na evolução do câncer do colo uterino (CCU) avançado e a nefrostomia percutânea guiada por ultrassonografia (NFT) é uma técnica bem estabelecida para a rápida desobstrução ureteral.

Objetivo: esclarecer os fatores relacionados à evolução ou não para óbito e qualidade de vida das pacientes com CCU avançado com complicações obstrutivas urinárias agudas e que, após desobstrução pela NFT, recuperaram fluxo urinário e função renal.

Método: foi realizado estudo transversal analítico descritivo, que avaliou dois grupos de pacientes com CCU submetidas à NFT [óbito (GO) e sobrevida (GS)], em um hospital público, referência para doenças oncológicas da região Norte do país.

Resultados: a creatinina sérica média inicial era >10 mg/dL pré-NFT e tornou-se <2 mg/dL após. Quanto à sobrevida, os pontos de corte de 8,7 g/dL de Hb e 27% de Ht melhor discriminaram a evolução dos grupos GO e GS ($p=0,0241$ e $p=0,0065$). Hipotensão se associou significativamente ($p=0,0037$) com a evolução para óbito. Variações na taxa de filtração glomerular, que já era reduzida em todos os casos, não se associaram aos níveis de Hb/Ht ou à evolução para óbito durante seguimento nefrológico.

Conclusão: a NFT permitiu a recuperação da função renal em 61,7% das pacientes com CCU, dispensando terapia de substituição renal. Níveis de Hb >8,7 g/dL e Ht >27% estiveram associados a maior sobrevida, e a hipotensão durante o seguimento associou-se com evolução para óbito.

Palavras-chave: obstrução ureteral, insuficiência renal crônica, nefrostomia percutânea, anemia, creatinina, sobrevida.

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