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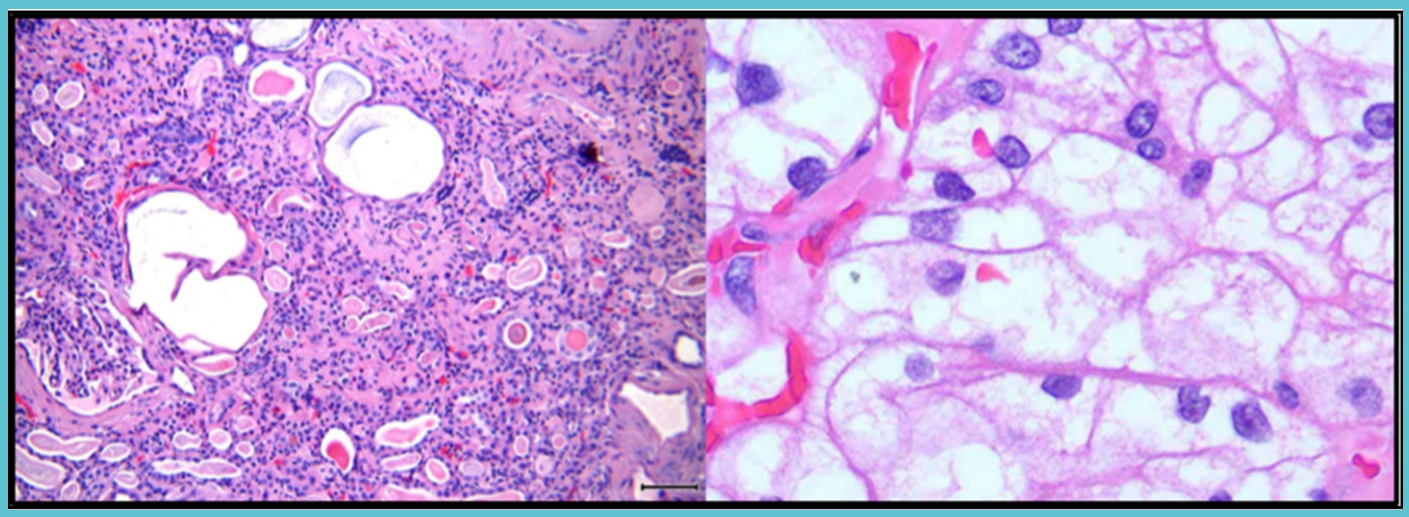

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Completion of Maintenance Bacillus Calmette-Guerin Therapy Might Prolong Recurrence-Free Survival in Patients with Non Muscle Invasive Bladder Cancer

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Abstract

***Objective*: The aim of our study was to compare recurrence-free survival between patients who completed treatment with maintenance Bacillus Calmette-Guerin (BCG) and patients who did not complete the planned treatment. *Materials and Methods*: Data on 115 patients with intermediate- and high-risk Non-Muscle Invasive Bladder Cancer (NMIBC) who were treated with BCG were available for analysis. Patients were categorized into 4 groups based on treatment duration: patients who completed three years of maintenance treatment, patients who stopped treatment while on maintenance, patients who were still on-treatment and patients who were treated with induction course only. *Results*: Of 115 patients, 86 were men and 29 were women with mean age of 67.8 (range 40 - 93) years. 51% had high-grade tumors and 49% had low-grade tumors. Seventy-three patients (63%) had multiple tumors. Thirty patients (26%) were treated with induction-only, 18 patients (16%) are on-treatment, 14 patients (12%) finished maintenance protocol and 53 patients (46%) discontinued treatment. Reasons for stopping treatment were disease recurrence in 13 patients and toxicity in 40 patients. 5-year recurrence-free survival was 100%, 63%, 60% and 56% in patients who completed maintenance treatment, stopped during maintenance treatment, were on-treatment and those who received induction only therapy, respectively. *Conclusions*: Patients should be encouraged to adhere to maintenance BCG treatment because of its favorable effect on recurrence-free survival probability.**

Keywords

Bladder Cancer, BCG, Induction Therapy, Maintenance Treatment

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1. Introduction

Non-Muscle Invasive Bladder Cancer (NIMBC) is defined as papillary tumors confined to the mucosa or invading the lamina propria and are classified as stage Ta and T1, respectively, according to the Tumor, Node, Metastasis (TNM) classification system. Flat, high-grade tumors that are confined to the mucosa are classified as CIS (Tis). These tumors can be treated by transurethral resection of the bladder (TUR-BT) with or without intravesical instillations.

Intravesical bacillus Calmette-Guerin (BCG) is currently regarded as the standard treatment after transurethral resection for patients with NMIBC. Several randomized-controlled trials have shown the superiority of adjuvant BCG over TUR-BT alone or combined with non-BCG adjuvant intravesical therapy [1]-[3]. As BCG induces immune response, researchers developed maintenance protocols that include long-term admission of intravesical BCG beyond the induction period. Indeed, most practical guidelines recommend maintenance BCG for 1 - 3 years [4]-[6]. Several studies have shown the superiority of maintenance protocols over induction-only [2] [7]; however, recent report demonstrated no difference between the two approaches [8].

The aim of this study was to assess recurrence-free survival probabilities in patients who received complete treatment with maintenance BCG compared with those who failed to complete the full regimen.

2. Patients and Methods

The study was approved by the hospital IRB committee. We retrospectively evaluated data on 115 patients with NMIBC who underwent TUR-BT and were treated with intravesical BCG in our department during 1999-2010 and were followed for at least 3 years.

Most patients underwent re-TUR-BT, mainly because of pathological stage T1 or high-grade cancer. Our BCG protocol include done course (6 weekly sessions) of induction therapy followed by 7 courses (3 weekly sessions) of maintenance therapy over 3 years as suggested by Lamm *et al.* [9].

BCG treatment was started two weeks following TUR-BT. Follow-up protocol included cystoscopy, urinary tract imaging and urine cytology. The first cystoscopy was done after completing induction with 6 intravesical instillations of BCG. If no evidence of recurrence was noted, a cystoscopy was done every 3 months for the first two years, every 6 months for years 3 - 5 and annually thereafter. Urine cytology was done on each cystoscopy visit. An upper urinary tract imaging using CT-or MR-Urography was done annually.

Patients were categorized into four groups: 53 (46%) patients who discontinued BCG while on maintenance, 18 (16%) patients who were on-maintenance with BCG, 30 (26%) patients who received induction therapy only and 14 (12%) patients who completed the planned treatment protocol with BCG.

The primary endpoint was recurrence-free survival probabilities. Kaplan-Meier survival curves were constructed to estimate the recurrence-free survivalprob abilities for each group. Breslow pair wise comparison test was used to compare Kaplan-Meier curves between all groups. A sub-analysis was also done based ontumor grade. A two-sided P-value of <0.05 was considered as statistically significant. Statistical analyses were done using SPSS v21.

3. Results

Among 115 patients, 86 (77%) were men and 29 (23%) were women. Mean age was 67.8 years (Median 69, range 40 - 93). Multiple tumors were seen in 73 patients (63.4%) and mean tumor size was 20.5 mm (median 19, range 5 - 100 mm). On histopathology, 59 (51%) patients had high-grade disease and 56 (49%) had low-grade disease. Regarding stage, 61 (53%) patients had Ta disease, 43 (37.5%) patients had T1 disease and 11 (9.5%) patients had Carcinoma *In Situ* (CIS). Patients' baseline clinical and pathological characteristics are summarized in **Table 1**.

Thirty patients (26%) received 6 instillations of induction only and discontinued treatment. Eighteen patients (16%) are being treated with maintenance BCG, 14 patients (12%) had completed all maintenance schedule and 53 patients (46%) had discontinued treatment while on maintenance. Median number of maintenance courses was 3 (range 1 - 7).

Reasons for stopping treatment were recurrence in 13 patients (24.5%) and toxicity (mainly urgency, dysuria, nocturia, fever, chills, arthritis, fatigue, abdominal pain) in 40 patients (75.5%). Most patients had grade I adverse events as described by the NCI-CTC [10] system and 3 patients had grade II adverse events.

With median follow-up of 77 months (IQR 58.93), disease recurrence was observed in 37 patients (32%). Median time to recurrence was 12 months (IQR 6.30). Of these 37 patients, 14 patients (38%) received induction therapy only, 9 patients (24%) discontinued maintenance treatment, 13 patients (35%) were on-maintenance treatment and only one patient (3%) was from the completed-treatment group. Treatment and recurrence data are shown in **Table 2**.

Table 1. Patients' baseline characteristics.

Age (years)	
Mean	67.8
Range	40 - 93
Sex (%)	
Male	89 (77%)
Female	26 (23%)
Ethnics (%)	
Jewish	101 (88%)
Arab	8 (7%)
Other	6 (5%)
Grade (%)	
High-grade	59 (51%)
Low-grade	56 (49%)
Stage (%)	
Ta	61 (53%)
T1	43 (37.5%)
CIS	11 (9.5%)
Tumors no. (%)	
Solitary	42 (36.5%)
Multiple	73 (63.5%)
Tumor size (mm)	
Mean	20.5
Median	19
Range	5 - 100

Table 2. Treatment and recurrence data.

Treatment group (%)	
Induction only	30 (26.1%)
Ongoing	18 (15.6%)
Stopped	53 (46.1%)
Finished	14 (12.2%)
Maintenance cycles*	
Median	3
Range	1 - 7
Reason for discontinuation (%)	
Toxicity	40 (75.5%)
Recurrence	13 (24.5%)
Recurrence rate (%)	37
Induction only	14 (38%)
Ongoing	13 (35%)
Stopped	9 (24%)
Finished	1 (3%)
Time to recurrence (mo)	
Median	12
Range	3 - 66

*Stopped-treatment group only.

Five-year recurrence-free survival was 100%, 63%, 60% and 56% in patients who completed the whole planned treatment, patients who discontinued treatment, patients who were on-maintenance treatment and patients who received induction only therapy, respectively. Patients who completed maintenance BCG had significantly higher recurrence-free survival rate compared to all other groups (P = 0.015), while no significant difference was seen between patients who discontinued treatment, patients who were on-treatment but didn't finish all courses yet and those who were treated with induction-only therapy. After stratification into high-grade and low-grade, 5-year recurrence-free survival was 87.5% and 100%, 71.4% and 72%, 53% and 69%, 53% and 59% in patients who finished treatment, patients who stopped treatment, patients who were on maintenance treatment and patients who received induction-only therapy, respectively. See **Figure 1**, **Figure 2**.

4. Discussion

NMIBC is a chronic disease with 5-year recurrence probability of up to 78%. Risk factors for recurrence are number of lesions, size of tumors, prior recurrence rate, stage, grade and concomitant CIS, with each additional risk factor multiplying the risk for recurrence [11]. These risk factors help stratify patients into 3 risk groups: low-risk, intermediate-risk and high-risk [4]. Patients with intermediate- and high-risk disease may have better recurrence-free survival if treated with adjuvant intravesical BCG [3] [12].

Several studies have evaluated the effect of maintenance BCG on the risk of disease progression. One large meta-analysis carried out by the EORTC-GUCG has evaluated 4863 patients in 24 different randomized control trials (RCTs). This study showed a reduction of 27% in the odds of progression with BCG maintenance treatment compared to control groups (TUR-BT alone or TUR-BT with non-BCG intravesical therapy) [7].

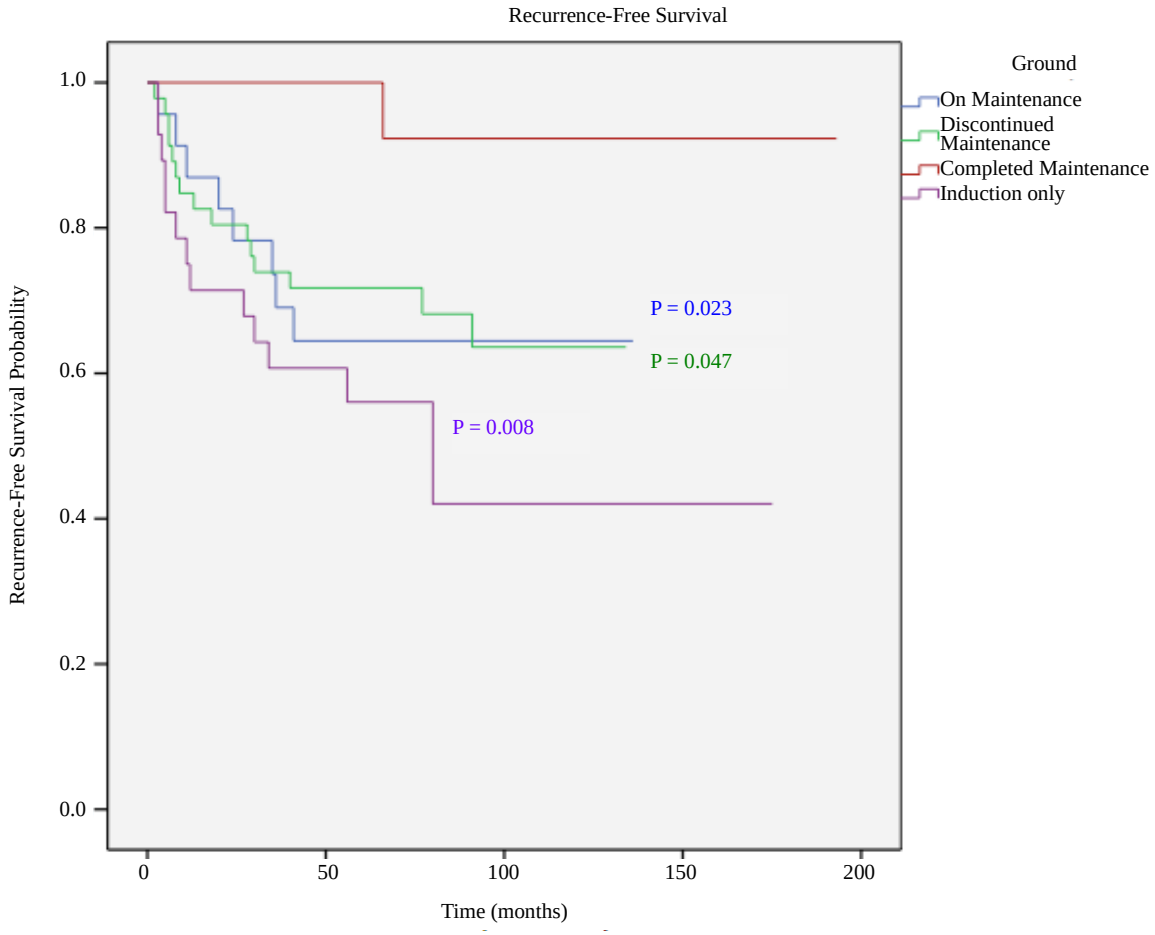

Figure 1. Overall recurrence free survival (RFS) shown as Kaplan-Meier curves in all groups. Breslow pairwise test was used to compare between KM curves. P-value indicates statistical significance compared to finished-treatment group.

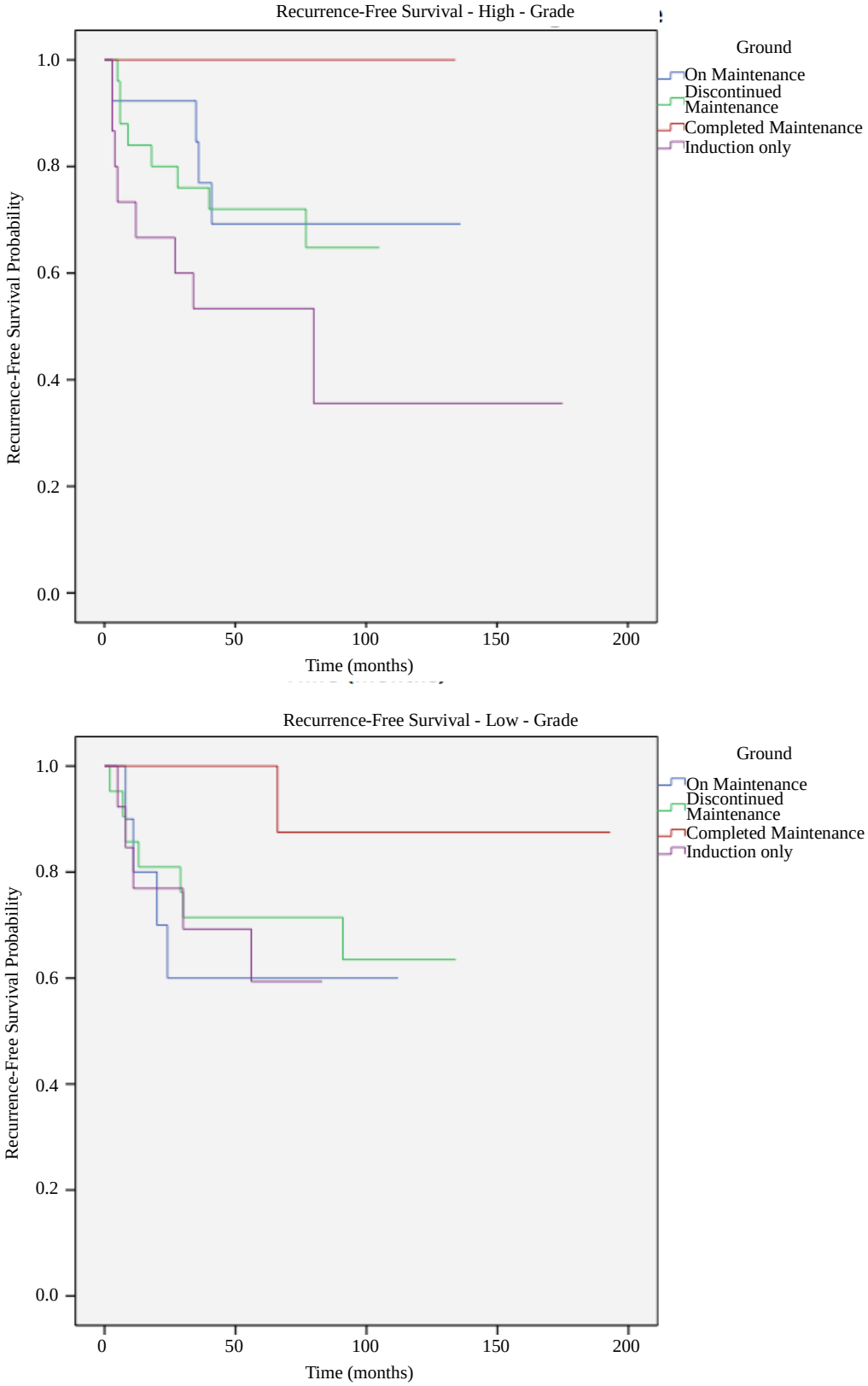

Figure 2. Recurrence-free survival adjusted to grade and shown as Kaplan-Meier curves. P-values are 0.011, 0.022, 0.046 for induction-only, ongoing and stopped-treatment groups, respectively, compared to finished-treatment group.

On the contrary, a meta-analysis of individual patient data was not able to confirm any statistically significant difference between MMC and BCG for progression, survival and cause of death [3].

The optimal number of induction instillations and optimal frequency and duration of maintenance therapy remain unclear [13]. In a recent large RCT, the EORTC has shown that 3 years maintenance with full dose BCG reduces the recurrence rate compared to one year in high- but not in intermediate-risk patients [12].

Although concerns about BCG-associated adverse events have been expressed in the past, more recent studies have shown that maintenance schedule is not associated with an increased risk of side effects comparing to an induction course [14]. Moreover, most of the side effects can be successfully managed and those requiring treatment termination are seen more often in the first year of therapy [15].

Herr *et al*. questioned the need for maintenance BCG, and showed 2-year and 5-year recurrence free-survival of 73% and 46%, respectively, rates that are comparable to previous studies using maintenance protocols [5]. However, most centers, including ours, still use maintenance intravesical BCG protocols for the treatment of intermediate- and high-risk NMIBC patients.

Our results showed that the effect of maintenance BCG on recurrence is in a direct duration-response relationship. Maximal long-term effect can be achieved only after several courses of BCG, ultimately after 3 years of maintenance therapy. This is demonstrated by the fact that no difference was seen between patients who didn't receive BCG compared to patients who were partially treated. We noted that patients who did not complete maintenance treatment, either because of toxicity or had not yet completed all treatment courses, had comparable recurrence-free survival rates that are significantly lower than patients who completed treatment. Conclusions cannot be made for the group of patients who was treated with induction-only because most of them stopped treatment as a result of disease recurrence.

In order to improve patients' adherence to the maintenance protocol in our center, we treat patients with oral antipyretics, analgesics and antibiotics when needed in order to reduce the irritative side effects. In some cases we reduce the dose or increase the interval between treatments sessions to help patients complete the treatment protocols.

Our study had several limitations. First of all, a small cohort that make it difficult to extrapolate the results on larger population. Another limitation is the retrospective nature and the fact that it is a non-randomized study; therefore, we cannot roll out the fact that there could be a selection bias. Further longer-term and larger studies are needed to prove, ultimately, the need for maintenance therapy, especially after several recent studies that question the need for it.

5. Conclusion

Our study showed that patients who completed maintenance therapy had a higher recurrence-free survival probability. Based on our results, maximal efforts should be done in order to encourage patients to adhere to the maintenance regime and to reduce the high rate of side effects related to the treatment in order to improve patients' tolerability and compliance.

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The Association between Autosomal Dominant Polycystic Kidney Disease and Renal Cell Carcinoma

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Abstract

Objectives: The relationship between autosomal dominant polycystic kidney disease (ADPKD) and renal cell carcinoma (RCC) is investigated to determine a link that would guide management due to elevated RCC risk. Current literature is inconclusive on this topic. Methods: This study is a retrospective chart review of patients having undergone nephrectomy. Those with pathology and history consistent with ADPKD were reviewed for presence of RCC. Results: The review at this institution revealed RCC in 18% of ADPKD patients who underwent nephrectomy. These rates are significantly higher than those found in the general population, and even greater than those would be expected in patients suffering end-stage renal disease (ESRD). Conclusions: Due to the increased prevalence of RCC in ADPKD, clinicians managing patients with ADPKD should maintain a high index of suspicion. Our data suggest a link between ADPKD and RCC, most likely at the genetic level. In light of this, we feel that further genetic research is needed to potentially discover the link between these two disease processes.

Keywords

Autosomal Dominant Polycystic Kidney, Chronic Kidney Failure, Genetic Variation, Nephrectomy, Renal Cell Carcinoma

1. Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal cystic disease

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affecting up to 1:400 people [1]. Approximately 5% of people in the United States with end stage renal disease requiring renal replacement therapy (RRT) can be attributed to an underlying pathology of ADPKD [2] [3]. Renal cell cancer (RCC), on the other hand, is a fairly rare disorder affecting only 10 - 20 per 100,000 [4]. The connection between these two diseases has been postulated, but currently, ADPKD is not held to be a risk factor for the development of RCC. This may be secondary to the limited number of cases, as well as confounding factors. It has been shown, however, that those with ADPKD develop RCC earlier than the general population and that many signaling proteins implicated in cancer are upregulated in individuals with ADPKD [5] [6]. Our institution reported the prevalence of RCC in nephrectomy specimens of ADPKD patients up to the year 2010 [7]. The goal of this study is to update the data and to review the current literature regarding this clinical entity.

2. Methods

After obtaining IRB approval (approval # L15-021), all nephrectomies performed in our institution from May 2010 to October 2014 were reviewed yielding 229 cases. World Health Organization criteria were used for classification of all cases [8]. Those cases with pathology and history consistent with ADPKD were included while those with renal cystic disease from all other causes were excluded. A total of 16 cases met the qualifications for ADPKD [9]. Pathology for these cases was reviewed for the presence of RCC.

Pubmed was systematically reviewed using “renal cell carcinoma” and “autosomal polycystic kidney disease” as keywords and subsequent survey for case reports and case series, yielding 42 papers published within the last 10 years regarding the incidence of RCC in ADPKD patients (see **Table 3** summarizing these papers). The vast majority of these papers state that there is no generally accepted association between ADPKD and RCC, but most do not refute the possibility due to lack of statistically significant numbers of patients in trials.

3. Results

16 cases of ADPKD were identified between May 2010 and October 2014 (**Table 1**). Of these cases there were 2 out of 16 pathology reports that revealed the presence of RCC (13%). The median age was 54 years. Of the 2 patients identified with RCC, one had a 10-year history of RRR, while the other had a 1-year history of RRT. The RCC subtypes identified were clear cell and mixed (clear cell, papillary, sarcomatoid).

In a prior ADPKD study from our institution by Lane *et al.*, 2 cases of RCC were found out of 6 cases of nephrectomy (**Table 2**) [7]. Combining their data with the current study gives a total of 4 cases of RCC among 22 nephrectomies (18%) from 2007 until 2014 at our institution.

Figure 1 illustrates a representative histological example of an ADPKD kidney specimen showing features of cysts and dysplastic ducts (**Figure 1(a)**), as well as harboring an area of renal cell carcinoma within the parenchyma of the same kidney (**Figure 1(b)**).

4. Discussion

A possible association between RCC and ADPKD was first suspected and described by Walters and Brasch in 1934 [10]. Their findings were initially considered to be coincidental, but over 60 case reports and case series have supported their hypothesis [6] [11]-[13]. The results from our institution’s case series endorse the same ideation. Despite this, some clinicians have continued to dispute any association between these two disease processes. Even in the recent literature, there is still no consensus regarding ADPKD and the associated risk for RCC [6] [11] [14]-[17].

When considering autopsies of deceased ADPKD patients, RCC is not listed under the most common causes of mortality [17]. Therefore, many clinicians believe that the issue of RCC in ADPKD patients is not relevant. In addition, the presence of RCC in the specimen is easily missed. The RCC tumor clusters can be small and easily “overlooked”, particularly if the pathologist is not suspicious of these lesions [6] [18]. In contrast to sporadic RCC, the diagnosis of RCC in ADPKD kidneys can only be made in surgical specimens. Imaging studies fail to confirm or rule out RCC, making this a more difficult diagnosis in these patients. Thus, the true prevalence and incidence in ADPKD patients cannot be determined. This may explain why some studies do not demonstrate any significant statistical support for the association of ADPKD and RCC.

Regardless which side of the discussion is favored, nearly all agree that the sample size is too small. There simply are not enough cases to statistically support either argument [6] [11] [18] [19]. This case series is intended

Table 1. Summary of clinical data and histopathological features of the patients who underwent unilateral or bilateral nephrectomy due to ADPKD from the years 2010 until 2014.

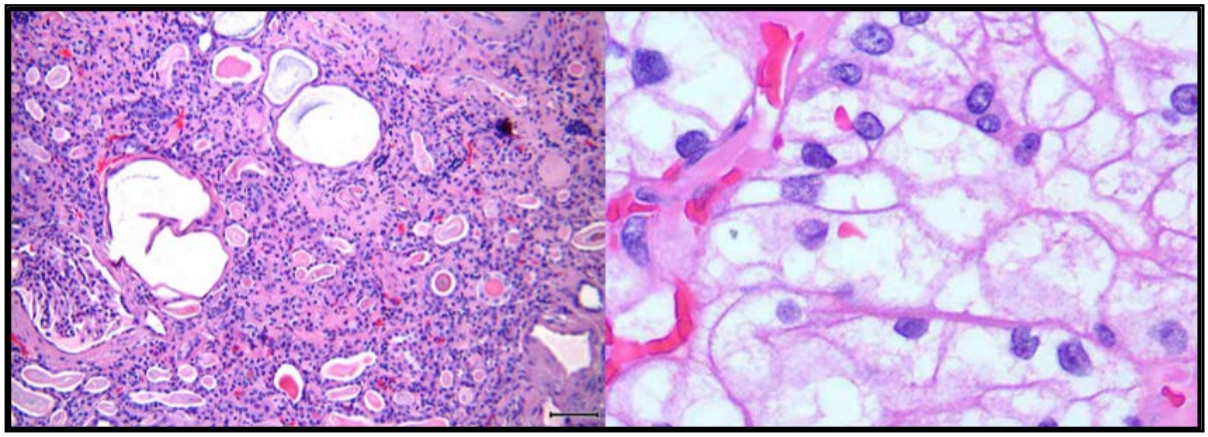
Age	Sex M/F	Ethnicity Hispanic = 0, White = 1 Black = 2, Other = 3	Year of Nephrectomy	Indication for nephrectomy Size = 1, Calcifications = 2 Solid mass = 3, Other = 4	Time on RRT† prior to nephrectomy (years)	RCC‡ No = 0 Yes = 1	RCC‡ features	Tumor Size (cm) L/R
59	M	1	7/2010	2	0	0		
57	F	3	7/2010	2	5	0		
53	F	1	8/2010	4	0	0		
68	M	1	2/2011	2	4.5	0		
58	F	1	2/2011	3,4-retroperitoneal bleed	10	1	Mixed (clear cell, papillary, sarcomatoid)	(6) L
61	M	1	5/2011	2	0	0		
57	M	1	5/2012	4-infections	0	1	Papillary Adenoma	(0.4) L
58	F	1	6/2012	3	0	0		
57	M	0	6/2013	4-recurrent hematoma	7	0		
57	M	1	7/2013	1	2.5	0		
58	F	1	12/2013	1	0	1	Papillary Adenoma	(0.3) L
67	F	3	1/2014	1, 2, 3	0	0		
43	F	0	2/2014	1	6	0		
45	M	1	5/2014	1	1	0		
44	M	1	8/2014	1	1	1	Clear Cell	(5) R
52	M	1	8/2014	1	0.25	0		

†Renal Replacement Therapy, ‡Renal Cell Carcinoma.

Table 2. Lists a previous series of ADPKD patients undergoing nephrectomy at our institution in the years 2007 through 2010. Three out of six patients had confirmed RCC. These data were published in 2011 [7].

Age	Sex M/F	Year of Nephrectomy	Indication for nephrectomy Size = 1, Calcifications = 2 Solid mass = 3, Other = 4	Time on RRT† prior to nephrectomy (years)	RCC‡ No = 0 Yes = 1	RCC‡ features	Tumor Size (cm) L/R
64	F	6/2010	1	2.5	1	Papillary Adenoma	(0.4) L/(0.4)R
59	M	5/2010	2	0	0	-	-
57	M	5/2009	3	3	1	Clear Cell	(1.1, 0.55) L/(0.2) R
41	F	11/2008	1	2	0	-	-
50	F	6/2007	1	1.5	0	-	-
51	M	5/2007	1	*	1	Clear Cell	(3.5) R

†Renal Replacement Therapy, ‡Renal Cell Carcinoma, *Data Not Available.



(a) (b)

Figure 1. (a) A representative example of a polycystic kidney composed of cysts in different sizes (hematoxylin and eosin staining; ×100); (b) Renal cell carcinoma with pleomorphic nuclei removed from a tumor nodule in the same kidney specimen as shown in **Figure 1(a)** (hematoxylin and eosin staining; ×400).

to expand the pool of data, so that sufficient numbers will be available to complete epidemiologic studies on this phenomenon in the future.

According to the National Cancer Institute SEER program, the incidence of sporadic RCC is estimated to be 21.02 per 100,000 in men and 10.4 per 100,000 in women [4]. Amongst these cases the most common variant of RCC is clear cell carcinoma, accounting for nearly 80%. This is followed by papillary carcinoma, which contributes 15% of the RCC variants [20] [21].

Irrespective of the variant diagnosed via specimen histology, all subtypes initially originate within the renal cortex and have common, well-established risk factors. Smoking, hypertension and obesity are considered weak risk factors for RCC; however, ESRD is unequivocally considered a major risk factor for this malignancy. Bonsib *et al*. reported rates as high as 8% of RCC in patients with ESRD or undergoing dialysis for an average of 9 years [17].

The association of RCC and ESRD is widely accepted in the literature [6] [11] [17] [18]. The prevalence of RCC in ESRD patients is significantly higher than the prevalence of sporadic RCC in the general population (by a factor of 1000), and therefore, ESRD is a well-established risk factor for this malignancy. Because the majority of ADPKD patients develop ESRD requiring long-term dialysis, some clinicians assume that their ESRD status alone is the only significant and relevant risk factor for RCC. On the contrary, numerous studies have demonstrated that the rates of RCC in ADPKD patients are still higher when adjusted for time spent on dialysis and compared with ESRD patients whose kidneys failed due to other causes than ADPKD [6] [18].

When compared to RCC, ADPKD is much more common in the general population. Genetic mutations associated with the disease are as common as 1 per 1000, or at least one hundred times more prevalent than RCC. There are three common mutations currently known and related to ADPKD pathogenesis: PKD1, PKD2, and PKD3. Chromosome 16 houses the mutation in PKD1, which accounts for 85% of APKD cases. PKD2, found on chromosome 4, is much less common [1]. According to current literature, the significance of determining the specific mutation helps stratify the risks and prognosis of disease progression. PKD1 mutations are associated with much earlier onset of ESRD than PKD2 [22].

While there is a much higher incidence of ESRD development in ADPKD patients, and ESRD leads to higher RCC risk, the data obtained at our institution supports the hypothesis that ADPKD patients still demonstrate higher rates of RCC than would be expected by ESRD alone. Furthermore, RCC in ADPKD patients develops at much younger ages (average 47 years) and is often bilateral (29%) and multicentric (25%) [12]. These rates are significantly higher than those found in sporadic RCC development, with 61 years being their median onset, 2% - 6% are bilateral, and only 5% are multicentric [12] [13] [22]. These clinical features of RCC in the ADPKD population are specific and unique, and the increased prevalence could be attributed to the associated ADPKD genetics and pathophysiology.

The data collected at our institution and presented in this papersupport this relationship with an 18% preva-

lence of RCC in ADPKD patients. Hajj and other clinicians described rates varying from 5% to 12% depending on the time frame of RRT. Although these rates are high, some researchers argue that they are low estimates. Soft tissue nodules, which may harbor RCC within the ADPKD specimen after nephrectomy, can easily be overlooked, in particular, when the clinician does not alert the pathologist that RCC is suspected. One purpose of this paper is to make clinicians and pathologists more attentive to this issue when submitting kidney specimens of ADPKD patients.

By restricting our epidemiologic pool to patients with nephrectomy, many proponents believe that the prevalence of RCC in ADPKD is underreported [6] [18]. Comparing these rates to the previously mentioned 0.021% prevalence of sporadic RCC in the population or the 4.8% prevalence of RCC in ESRD patients further supports the hypothesis of strong association between ADPKD and RCC.

With the literature equivocal regarding an increased risk for RCC in ADPKD, there is a lack of clear guidance regarding early nephrectomy in patients who develop new or growing soft tissue nodules within their kidneys. **Table 3** provides an overview of the body of literature published on the topic "RCC in ADPKD" [11] [12] [18] [23]-[30]. A review of these studies shows that the majority of investigators and clinicians acknowledge a link between ADPKD and the risk for RCC beyond the current risk associated with ESRD.

Table 3. Literature review.

Age	Sex	Involvement L/R	RCC[‡] pathology	RRT[†] (years)	Citation
58	M	Bilateral	Papillary Renal Cell Carcinoma	0	[11]
32	M	Bilateral	Papillary Renal Cell Carcinoma	0	[11]
45	M	R	Clear Cell and Papillary Renal Cell Carcinoma (17 foci)	10	[12]
*	M	L	Papillary Non-Invasive Urothelial Carcinoma	0	[18]
*	M	L	Multi-locular Cystic Renal Cell Carcinoma	5	[18]
*	M	Bilateral	Papillary Renal Cell Carcinoma	0	[18]
*	M	R	Papillary Renal Cell Carcinoma (2 foci)	2.5	[18]
*	M	L	Clear Cell Renal Cell Carcinoma	1	[18]
*	M	L	Papillary Renal Cell Carcinoma	3	[18]
*	M	R	Clear Cell and Papillary Renal Cell Carcinoma	3	[18]
*	M	L	Papillary Renal Cell Carcinoma	5	[18]
*	M	R	Papillary Renal Cell Carcinoma (2 foci)	2.5	[18]
*	M	R	Clear Cell Renal Cell Carcinoma	0	[18]
*	F	R	Clear Cell Renal Cell Carcinoma (1 focus), Papillary Adenoma (<0.5 cm, current guidelines classified as adenoma)	7	[18]
*	F	L	Papillary Adenoma (<0.5 cm, current guidelines classified as adenoma)	0	[18]
*	M	R	Cysts with Polypous and Papillary Proliferation	0	[18]
*	M	R	Cysts with Polypous and Papillary Proliferation	4	[18]
*	F	R	Cysts with Polypous and Papillary Proliferation	0	[18]
*	M	L	Papillary Renal Cell Carcinoma	0	[18]
67	F	L	Clear Cell Renal Cell Carcinoma	11	[23]
57	M	L	Papillary Renal Cell Carcinoma	7	[24]
47	M	R	Clear Cell Renal Cell Carcinoma	*	[25]
58	F	R	Clear Cell Renal Cell Carcinoma	0	[26]
57	M	L	Clear Cell Renal Cell Carcinoma	10	[27]
58	M	Bilateral	Papillary Renal Cell Carcinoma	19	[28]
68	F	L	Clear Cell Renal Cell Carcinoma	8	[29]
47	M	Bilateral	Renal Cell Carcinoma (unspecified)	0	[30]

[†]Renal Replacement Therapy, [‡]Renal Cell Carcinoma, [*]Data Not Available.

According to our data, approximately 18% of these ADPKD cases harbor RCC within their kidneys. Therefore, early nephrectomy should be seriously considered, and when possible, bilaterally in patients with nonfunctioning native kidneys. These statistics again suggest a genetic link between ADPKD and RCC. This presents a new and exciting challenge to explore the genetics of these two diseases more closely.

The main limitations of our study are related to the current diagnostic shortcomings and limited statistical data. By relying upon histopathology reports on surgical specimens, the observed prevalence is grossly underestimated and does not represent the true prevalence in all ADPKD patients. Until a less-invasive modality can prove as accurate and even timelier, the field will continue to depend on the data of surgical candidates in ADPKD. As with all rare diseases, time will provide additional data. The continual publishing of case reports and series on this topic will expand the foundation of medical knowledge and we encourage others to continue to do so. It is our hope that then physicians will be equipped with the tools and knowledge base to accurately and effectively manage RCC in ADPKD patients.

Conflict of Interest

None of the contributing authors have any conflict of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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Acute Urinary Retention among Adult Men at Bobo-Dioulasso University Teaching Hospital: Epidemiology, Aetiologies and Initial Management

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Abstract

We conducted a cross-sectional study between February 1st, 2012 and September 30, 2012 at Bobo-Dioulasso University Teaching hospital. The target population was all patients seen at the emergency services for acute urinary retention. Among the 155 patients admitted for urological emergencies, 104 (67.1%) had acute urinary retention. The average age of patients was 65 years, ranging from 23 to 89 years and the majority was more than 60 years old (77.8%) and lived in rural areas (64.4%). Prostate tumor pathology and urethral stricture were the most frequent diagnosis, and the renal function was impaired in 33.7% of cases. Urethrovesical drainage, cystocatheterism, and suprapubic cystostomy were the treatment approach in 56.0%, 28.0% and 15.2% of the cases. Acute urinary retention is the most common urological emergency and many complications are associated with urethrovesical sounding. These complications should therefore be prevented by improving acute urinary care.

Keywords

Acute Urinary Retention, Epidemiology, Management, Prostate

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1. Introduction

Acute urinary retention (AUR), also known as full bladder urinary retention, is the sudden and complete inability to pass urine despite an irresistible need. It is the most frequent reason for consultation in urology. It epitomizes the urological emergency, and requires immediate treatment through catheterization or cystocatheterism [1]. In developed countries, its management is part of a well-established medical emergency practice. However, in developing countries such as Burkina Faso, the management of the complete urine retention encounters many difficulties [2]-[4]. The purpose of this study is to determine the frequency of the acute urinary retention in at the Sourou Sanou Teaching Hospital and to assess the etiologies and to describe its initial management in that health facility.

2. Materials and Methods

It was a descriptive cross-sectional study, carried out from February 1st, 2012 to September 30th, 2012 in the medical and surgical emergencies division of Bobo-Dioulasso University Teaching hospital. The target population was all patients seen at the emergency services for acute urinary retention or patients who are already supported in another health centers. After a brief physical cross-examination, we fill our data collection form. Depending on the general condition of the patient, he may be admitted as in patient or managed on out-patient basis. The following parameters were studied: frequency, epidemiological characteristic of patient, a etiological diagnosis, emergency care modalities.

3. Results

During the study, 155 patients were admitted for urological emergencies, 104 (67.1%) had acute urinary retention. The incidence was 12 cases per month.

The average age of the patients was 65, ranging from 23 to 89 years. Patients over the age of 60 years formed the majority (77.8%). Farmers were most predominant in the study; they represented 75% of the patients studied. Majority of the patients (64.4%) were from rural areas. In the medical history, the notion of UTI was noted in 83.8% of cases and the bladder catheterization in 86.4% of cases.

The average time interval between the onset of urinary retention and patient admission to the emergency department was 22 hours. In the study, 97% of the patients had lower urinary tract symptoms (LUTS) prior to urinary retention.

On digital rectal examination, the prostate was enlarged in 77.9% of the cases. It had benign aspect in 68.3% of the cases and malignant aspect in 9.6% of the cases.

About the etiologies of acute urinary retention, benign prostate enlargement (BPE) and urethral stricture were the two common causes respectively in 62.5% and 15.4% (**Table 1**).

Acute urinary retention should be managed by immediate and complete decompression of the bladder through catheterization. **Table 2** presented the distribution of patient according to emergency management and the practionner who perform the procedure. Urethral catheterization and suprapubic cystostomy were the main procedures doing for bladder drainage.

Table 1. Distribution of patients according to the etiological diagnosis.

Etiologicdiagnosis	Frequency	Percentage (%)
Benign Prostate Enlargement	65	62.5
Urethral stricture	16	15.4
Prostate cancer	9	8.6
Disease of the bladder neck	6	5.8
Lowurinary tract trauma	5	4.8
Urolithiasis	2	1.9
Bladder tumor	1	1
Total	104	100

Diagnostic testing in patients was done in our patients with urinary retention such as serum blood hemoglobin, creatinine and blood sample for measurement of serum prostate-specific antigen level was obtained. The hemoglobin level was lowered in 65.4% of cases. Moreover 63.5% of patients had moderate anemia (**Figure 1**). The third of patient (33.7%) presented renal function impairment (**Figure 2**). Blood serum PSA level was obtained in 90 cases. In 43.3% of cases, PSA level is more than 4 ng/ml. The distribution of patient based on PSA level was shown on **Figure 3**.

Ultrasonography was done by 86 patients. Ultrasound has a very important role in imaging of the lower urinary tract because its implicity and no ionizing radiation used. The ultrasound was contributive to the etiological diagnosis in 96.5% as stated in **Table 3**. Urinary retention was caused by BPH in 82.6% of patients.

Retrograde urethrography (RUG) is performed to visualize the adequately distended anterior urethra, and voiding cystourethrography (VCUG) is then performed to properly evaluate the posterior urethra. In all, 26 patients had done this imaging. The results were abnormal in 24 cases (92.3%). The RUG revealed a stenos is in 69.2% of cases. Distribution of the patient according to RUG and VCUG is presented in **Table 4**.

4. Discussion

The prevalence of acute urinary retention among urological emergencies was 67.1%. This high prevalence in our study may be due to the fact that our patients do not consult for lower urinary tract symptoms (LUTS). This could be due to the lack of information about these conditions, the lack of economic resources, and an inadequate coverage of health facilities. The average age of our patients was 65 years, ranging from 23 to 89 years.

Table 2. Distribution of patients according to emergency management.

Health Worker	Management				Total
	Urinary Catheter	Suprapubicpuncture	Cystocatetherism	Open cystostomy	
Nurse	64	1	0	0	65
Extern	5	0	0	0	5
Internship	1	0	9	0	10
Assistant	7	0	0	6	13
General Practitioner	0	0	0	11	11
Total	77	1	9	17	104

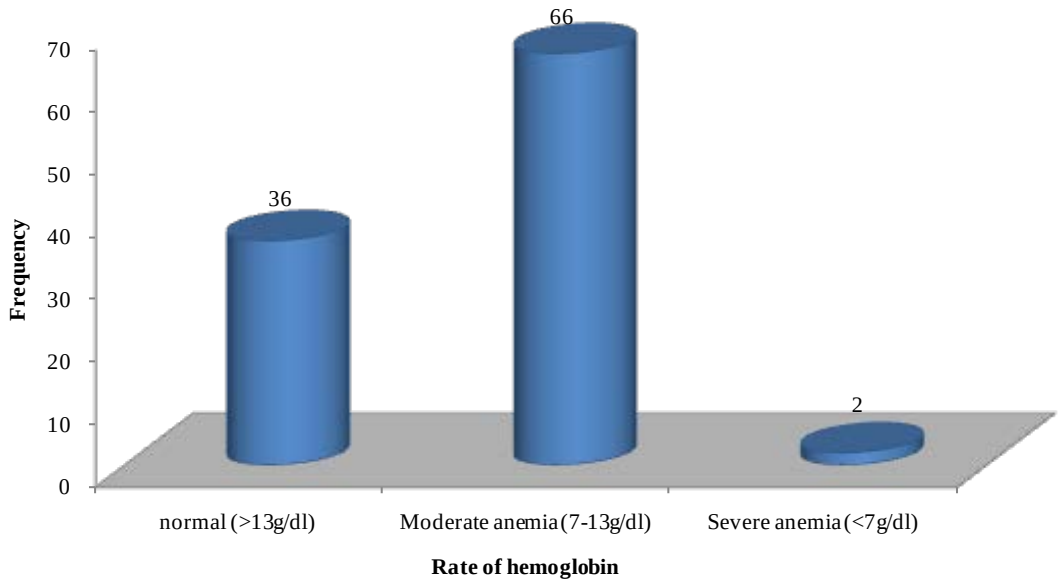

Figure 1. Distribution of patients based on the hemoglobin level.

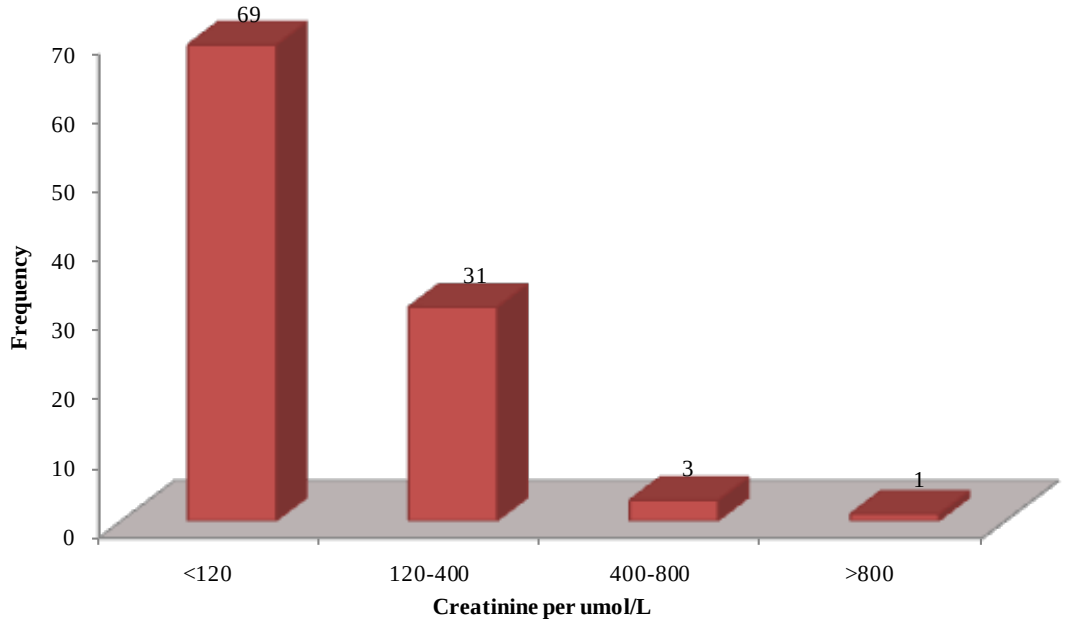

Figure 2. Distribution of patients based on the creatinine level.

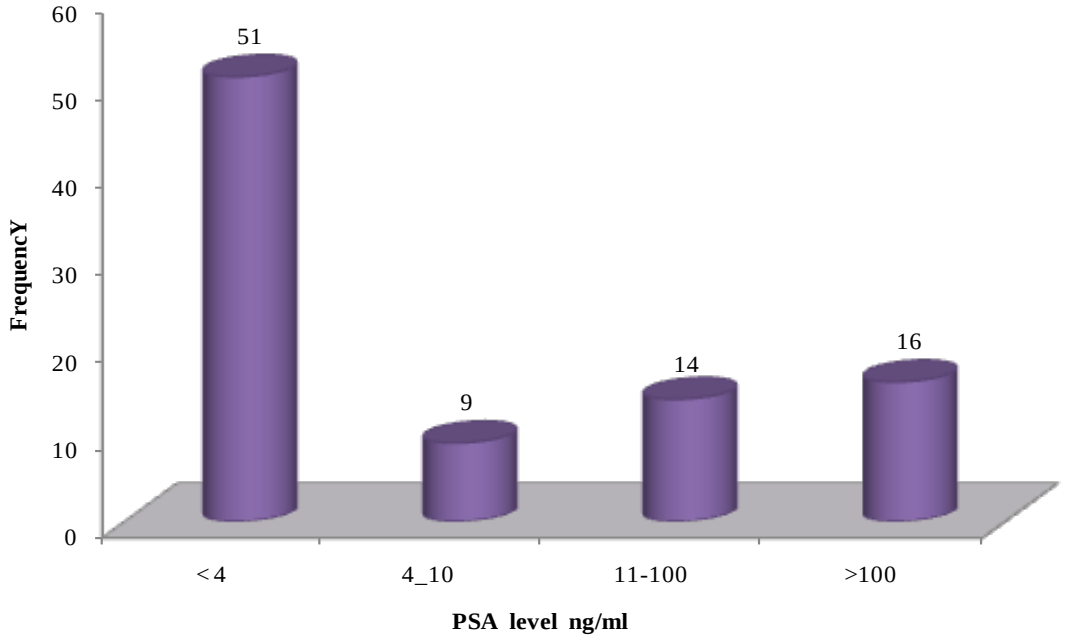

Figure 3. Distribution of patients based on PSA.

The most represented age group was that of 61 - 75 years. This finding is congruent with Diallo AB *et al.*'s figures in Conakry at Guinea and Senegalese authors in their work on acute urinary retention [4] [5].

The average time interval between the onset the acute urinary retention symptoms and the patient admission to the hospital was 22 hours. We believe that this timeframe is too long and could be explained by the fact that many of our patients still use traditional treatment for socio-economic reasons.

Prostate tumor pathology was the most frequent diagnosis, and this is justified by the old age of our patients. The renal function was impaired in 33.7% of cases. This deficiency may be related to the insidious onset of obstructive kidney disease culminating in the acute urinary retention, self-medication and the use decoctions of plants which usually bear renal toxicity.

Table 3. Distribution of patients according to the results of ultrasound.

Ultrasoundfindings	Frequency (n)	Percent (%)
Normal	3	3.5
Benign Prostate Enlargement	71	82.6
Prostate cancer	10	11.6
Chronicprostatitis	1	1.5
Bladdertumor	1	1.5
Total	86	100

Table 4. Distribution of patients according to the retrograde urethrography (RUG) and voiding cystourethrography (VCUG) results.

Site of stricture	Frequency (n)	Percent (%)
Normal	2	7.7
Bladder neck disease	6	23.1
Posteriorurethra	5	19.2
Bulbar urethra	8	30.8
Narrowing of the penile urethra	3	11.5
Multiple urethralstricture	2	7.7
Total	26	100

Anemia was noted in 65.4% of the cases. Plausible reasons for this high frequency of anemia include hematuria found in several diseases, inadequate food intake related to the advanced age of our patients, renal failure. As our country is in the area of malaria endemicity, this could contribute to the low levels of hemoglobin observed in these patients.

The UCR revealed a stenosis in 69.2% of cases. The location of the stenosis was bulbar (30.8%), membranous (11.5%), penile (16.7%) ormultiple (7.7%). Several authors have also noted a high incidence of stenosis at the bulbar and membranous portions [6] [7].

Ibrahima Ga *et al* and Oguike *et al*, [8] [9]. both studies conducted in Nigeria, reported similar proportions with respectively 38.8% and 35.3% for bulbar location and only 10.4% and 10.3% for the penile location.

The only treatment that prevails in the acute urinary retention is the drainage of urine in emergency service. Urethrovesical catheterization, cystocatheterism and suprapubic cystostomy were the treatment approach in 56.0%, 28.0% and 15.2% of the cases. These findings were similar to reports from several series. Diallo and colleagues at Conakry in their serie had recorded 69.6% of urethrovesical catheterization and 30.4% cystostomy urethrovesical [4] [10] [11].

Catheterization is thus the most frequently method used for the drainage of AUR as directed, unless contraindicated [12]. However, it is erroneously considered as a trivial act, and several steps are neglected during its implementation, resulting in immediate or long term complications [13] [14]. The Foley catheter is the most commonly used for the catheterization; its material and the long term use could cause irritation of the urethral mucosa with a plausible local inflammation that may cause a stenosis in the medium term.

In addition, the majority of patients require surgery and will have to wear the device for several months while waiting for surgery. During this waiting period these patients are exposed to urinary infections and the deterioration of their lives standards. This delineates the difficulties encountered in the acute urinary retention and its management in our setting.

5. Conclusion

AUR is the most common urological emergency. Care in emergency unit is medical and surgical through bladder drainage and urethral sounding; it is the most frequently used approach. Many complications are associated

with urethrovesical sounding such as urethritis, urethral strictures and urinary tract infections. These complications should therefore be prevented by improving AUR care and by avoiding trauma of the urethra sounding, by increasing the capacity of our health units in general, and more specifically urology units for a better AUR care.

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Abbreviations

AUR: Acute Urinary Retention
BPE: Benign Prostate Enlargement
CHU Souro Sanou: Sourou Sanou University Teaching Hospital
RUG: Retrograde Urethrogram
LUTS: Lower Urinary Tract Symptoms
PSA: Prostate Specific Antigen
UTI: Urinary Tract Infection
VCUG: Voiding Cystourethrography

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Diagnostic and Analysis of Human Sperm Characteristics Using Fourier Transform Infrared Spectroscopy

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Abstract

A spectroscopic method for human sperm evaluation and characterization using Fourier Transform Infra Red (FTIR) is presented. The high sensitivity of FTIR to changes in chemical structure and arrangement of molecules and proteins makes it a powerful diagnostic tool. Our experimental results show that a simple MIR (400 cm^{-1} - 4000 cm^{-1}) transmission spectrum of a human sperm is very fast and can be used to determine the level of structure, compare to conventional LAB tests. No sample preparations are required, the semen has to be put on a special ZnSe substrate and inserted into the measurement compartment of the FTIR. Furthermore, this method can distinguish between immature sperm cell to white blood cell which by using a microscope is difficult and requires experience.

Keywords

Human Sperm, FTIR, Spectroscopic Measurements

1. Introduction

Diagnostics and analysis of human sperm are required as part of couples infertility investigation *and* treatments. It is also used to test human donors for sperm donation. The conventional tests done today are not perfect, time consuming and very expansive [1]. Furthermore, those tests are inaccurate since it depends on the experience of the lab technician [1].

Fourier Transform Infra-Red (FTIR) is used when measurements of optical properties of materials is required. Materials have unique molecular structures that cause them to absorb or transfer EM radiation as a function of radiation frequency [2]. This is due to molecular vibrations, rotations and electron spin flips. **Table 1** shows the different types of absorption resonances.

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Table 1. Transition type according to MIR, FIR and MMW spectral bands [2].

Type of Radiation	Frequency Range (Hz)	Wavelength Range	Wave Number [cm^{-1}]	Type of Transition
Mid infrared	10^{13} - 10^{14}	25 μm - 2.5 μm	400 - 4000	Molecular vibrations
Far infrared Millimeter waves	3×10^{11} - 10^{13}	1 mm - 25 μm	10 - 400	Molecular rotations, electron spin flips
Microwaves Radio waves	$<3 \times 10^{11}$	>1 mm	<10	Nuclear spin flips

The FTIR can measure transmission and refection in wide band of wave numbers 5 cm^{-1} - 10,000 cm^{-1}. Optical properties of solids, liquids, gasses and powders can be measured using the FTIR [2]. Since it has high sensitivity to changes in the chemical structure of the samples, it makes the spectral measurements attractive compare to X-ray diagnostics or other chemical conventional diagnostic methods. The principle of operation is based upon a Michelson interferometer with one displacement mirror and a fixed mirror. Sophisticated FFT procedure is used to obtain the signal as function of wave number [2].

Spectral measurements with Fourier Transform Infra Red (FTIR) are used to characterize the structure and composition of biomolecules [3]-[6]. Additional feasibility of this application is to diagnose different cancer types such as colonic cancer [7], lung cancer [8], malignant cancer fibroblast [9] and breast cancer [10]. FTIRs were used to investigate blood components in order to characterize infections disease in humans [11]. No sample preparation is required and the time required per sample is in the order of minutes and less. The diagnostic and analysis can be carried out for many samples in sequence.

In this publication we present our recent research in characterizing semen sample using FTIR spectroscopy in the Mid Infra Red (MIR) range. The components of the semen liquid include:

- Approximately 200 to 500 million spermatozoa—(also called *sperm* or *spermatozoans*), produced in the testes, and released by ejaculation
- Amino acids, citrate, enzymes, flavins, fructose (the main energy source of sperm cells, which rely entirely on sugars from the seminal plasma for energy), phosphorylcholine, prostaglandins, (involved in suppressing an immune response by the female against the foreign semen), proteins, vitamin C—produced in the seminal vesicle
- Acid phosphatase, citric acid, fibrinolysin, prostate specific antigen, proteolytic enzymes, zinc (serves to help to stabilize the DNA-containing chromatin in the sperm cells. A zinc deficiency may result in lowered fertility because of increased sperm fragility. Zinc deficiency can also adversely affect spermatogenesis.)—produced by the prostate.
- Galactose, mucus (serve to increase the motility of sperm cells in the vagina and cervix by creating a less viscous channel for the sperm cells to swim through, and preventing their diffusion out of the semen. Contributes to the cohesive jelly-like texture of semen.), pre-ejaculate, sialic acid—produced by bulbourethral gland.

All these components have influence on the semen function. Thus investigations of the optical properties of semen liquid can detect changes in the quantities and qualities of the samples. Preliminary measurements of optical properties of semen were made [12]. Those measurements show high absorption at 1650 cm^{-1} which corresponds to Amid 1 and 1545 cm^{-1} which corresponds to Amid 2 (see **Figure 1**).

In this research we characterize spectrally 80 semen sample using the FTIR. We also compared those optical results to standard semen analysis method [13] in the Male Infertility Center at Barzelai Medical Center, after receiving Helsinky approval.

2. Experimental Results

The semen samples were applied on a special ZnSe substrate. The ZnSe is transparent in the band 800 cm^{-1} - 4000 cm^{-1} where the semen has absorption lines. The substrates with the semen were installed inside the sample compartment of the FTIR system. **Figure 1** shows the absorption spectrum of normal human semen in the band 800 cm^{-1} - 4000 cm^{-1}. The absorption lines of Amid1 (1650 cm^{-1}) and Amid2 (1545 cm^{-1}) evolving from N-H, C=O and C-H connections are shown [14]. In Addition there are some weak absorption lines at 1245 cm^{-1}, 1450 cm^{-1}, 1310 cm^{-1} and 1390 cm^{-1} evolving from α-helical protein. More absorption lines are depicted in **Figure 1**.

In order to investigate the absorption lines of semen with different motilities we prepare three set of semen.

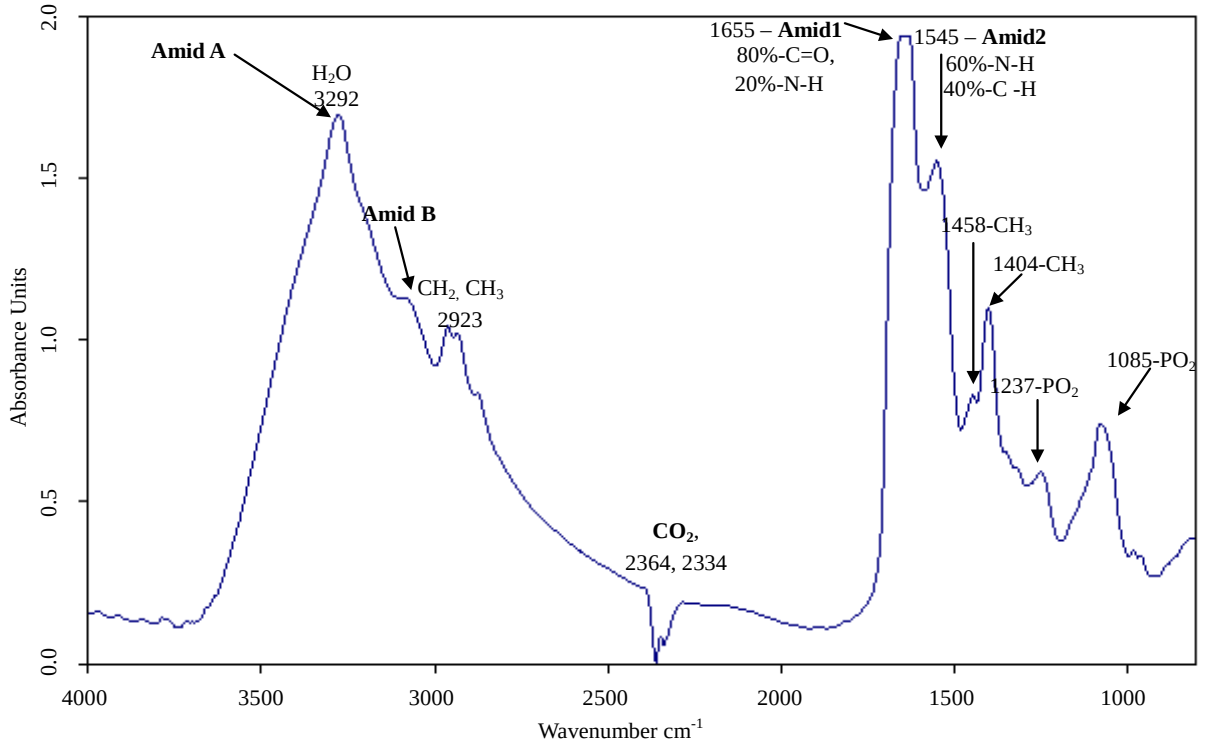

Figure 1. Absorption spectrum of normal human semen in the band 800 - 4000 cm^{-1}.

Those semen were selected and grouped shortly after performing conventional diagnostic and analysis. The first set includes 8 normal semen motility samples the second includes 7 samples of 30% - 50% semen motility and the third includes 65 sample of less than 30% semen motility. The samples were put on the top of special ZnSe substrate and inserted into the FTIR measurement compartment. In this study, the spectral region between 800 - 1800 cm^{-1} was investigated since it has many absorption lines as can be seen in **Figure 1**. **Figure 2** shows the average absorption lines and the standard deviation of those three sets where the normal semen motility is in blue, the 30% - 50% semen motility in green and lower than 30% semen motility, in red.

The spectra of **Figure 2** are with good agreement with the literature and with **Figure 1**. Note that the red line (less than 30% motility) in less absorbing than the blue and green lines which indicates differences in the molecular concentration and structure.

3. Discussion

The FTIR was found to be an efficient diagnostic tool for the structure and the composition of biomolecules [2]. Previous researches with FTIR proved feasibility to characterize biological cell with high reliability [6]-[11], therefore we evaluated the spectroscopic characteristics in semen of fertile and infertile men. The semen (ejaculate) structure is derived from seminal plasma and cells, which determine the absorption spectrum by similarity to cells and blood plasma [10] [11]. Different compound of semen samples characterize in different sperm motility and concentration for example:

- Additional cells and different compound of seminal plasma can be in the semen sample due to prostate and sperm vesicle.
- Modification in the sperm cell volume in the testis, or obstacles between the testis to urethra cause to different sperm mobility and concentration in the ejaculate.
- Infection in the sperm blister and prostate cause to different in the seminal plasma and sperm cells.

The absorption spectrum of seminal plasma and blood plasma are different because of the volume of proteins, hormones and electrolytes. The sperm cell motility in the ejaculate categorizes the group of the samples (Fertile and Infertile). Execute baseline correction and normalization according to Amid1 spectrum absorption allow to revaluate the quality and the quantity of the semen sample. There is no direct correlation between specific wave

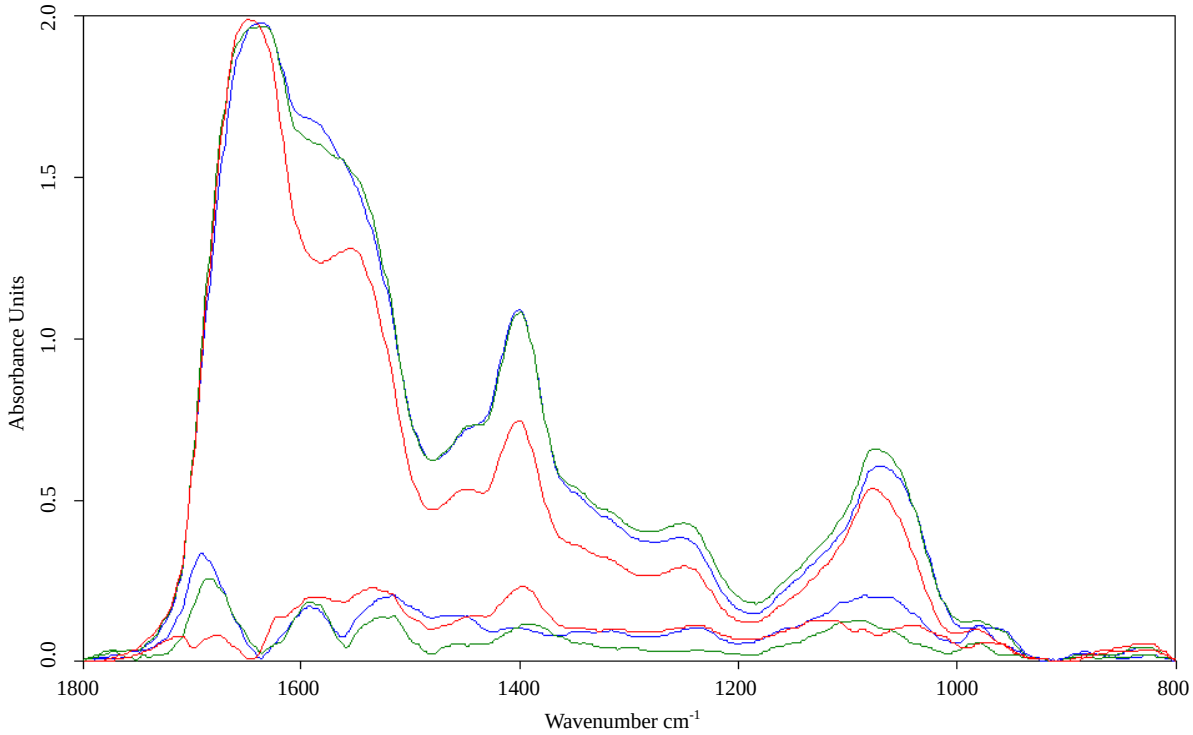

Figure 2. Absorption spectrum and standard deviation of three sets of different semen motility 1) normal blue line 2) 30% - 50% green line and 3) less than 30% red line.

numbers absorption to motility parameter, however the spectrum absorption is continuous 1700 - 800 cm^{-1}. The absorption spectrum can receive from chemical reaction that found in the cells and in the seminal plasma, changes in the seminal plasma or in the cells can cause to identify absorption spectrum although that the source of the change is different. In the future it is important to measure the absorption spectrum of all the semen components individually in order to compare the absorption spectrum of specific component that contain proteins, amino acids and chemical connection to references absorption spectrums, the purpose is to notice if we can get more remarkable different curves in the absorption spectrum. These curves enable us more accuracy identification of substance in the seminal plasma and in sperm cells. The spectroscopy can give additional information on sperm quality after treatment of infertile men and can guide to better methods of characterizing and treating patients. The characterization of DNA, important structure of nucleus and sperm tail can help to select a single sperm with better potential for injection in vitro fertilization. This method can help to determine changes in the sperm cell as results from freezing and thawing before surgical treatment, or in vitro fertilization. Based on the capability of the method to identify specific chemical and molecular connections, we can assist to characterize the different compositions of cells inside the testis biopsy in order to understand the testis cells characteristics that are a part of the spermatozoa process, for improving the quantity and quality in sperm cells production.

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