Original Article

Lessons Learned from the POUT Trial: Adjuvant Chemotherapy does Improve the Outcomes of Patients Treated with Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma

Abstract

Introduction: The management of patients with upper tract urothelial carcinoma (UTUC) is challenging, with radical nephroureterectomy (RNU) being the gold standard of treatment for high-risk disease. The role of chemotherapy is unclear. The POUT trial is a multicenter UK effort that addresses whether adjuvant chemotherapy improves disease-free survival (DFS) in patients with locally advanced and/or node-positive UTUC. **Methods:** The POUT trial enrolled 262 patients with UTUC (pT2-T4, N0-3, and M0) between 2012 and 2017. The patients were randomized (1:1) to four cycles of adjuvant gemcitabine–cisplatine (gemcitabine–carboplatin if GFR 30–49 ml/s) or surveillance following RNU. The patients were followed with cross-sectional imaging and cystoscopy every 6 months for the first 2 years and then annually for 5 years. The primary end point was DFS, whereas recurrence-free survival (RFS), overall survival (OS), toxicity, and quality of life (QoL) were the secondary end points. **Results:** The intent-to-treat analysis was conducted in 262 patients (131 chemotherapy and 131 surveillance). Among the patients treated with chemotherapy, 66% were offered gem-cis, while 68% completed successfully the four planned chemotherapy cycles. Approximately 50% of the patients undergoing chemotherapy developed Grade 3 or greater adverse events. A significant improvement in DFS (hazard ratio [HR]: 0.49 [confidence interval (CI): 0.31–0.76], $P = 0.001$) was observed at a median follow-up of 17.3 months. Considering the secondary end points, adjuvant chemotherapy was also associated with an improvement in RFS (HR: 0.49 [CI: 0.30–0.78], $P = 0.02$). Following adjustment for nodal involvement, the difference was more pronounced with a HR: 0.47 (CI: 0.30–0.74), $P = 0.001$. A difference in the OS curves favoring the adjuvant chemotherapy arm was noticed, but the difference remained nonsignificant due to short follow-up. **Conclusions:** The POUT trial provides exciting and convincing Level I evidence on the benefit associated with adjuvant chemotherapy administration in patients with locally invasive or node-positive UTUC.

Keywords: *Adjuvant, chemotherapy, nephroureterectomy, randomized, surveillance, upper tract urothelial carcinoma*

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Introduction

The management of patients with upper tract urothelial carcinoma (UTUC) is challenging due to the lack of high-level evidence, which results from the disease's overall rarity. The standard-of-care treatment for patients with high-risk disease (high grade or invasive) is radical nephroureterectomy (RNU), with some advocating for the added use of neoadjuvant or adjuvant platinum-based chemotherapy.[1,2] The added benefit of platinum-based chemotherapy in patients with locally invasive UTUC has been mostly extrapolated from the muscle-invasive bladder cancer literature and supported by several retrospective and population-based reports. Alison Birtle *et al*. reported the results of the first randomized clinical trial in the field assessing the added benefit of adjuvant platinum-based chemotherapy administration (ASCO-GU18, EAU 2018).

Materials and Methods

To start with, the authors have to be warmly congratulated for doing what many considered undoable in the field of this rare disease UTUC. The POUT trial, a multicenter UK effort, enrolled 262 patients with locally advanced and/or node-positive UTUC (pT2-T4 N0-3 M0) between 2012 and 2017. The patients were

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randomized (1:1) to four cycles of adjuvant gemcitabine–cisplatin (gem-cis)/gem–carboplatin (GFR 30–49 ml/min) or surveillance following RNU. Patients with a GFR <30 and those with incompletely resected macroscopic disease were excluded from the trial. Patients were followed up closely with cross-sectional imaging and cystoscopy every 6 months for the first 2 years and transitioned to annual follow-up for a total of 5 years. The primary end point for the trial was disease-free survival (DFS), with recurrence-free survival (RFS), overall survival (OS), toxicity, and quality of life (QoL) being the secondary end points.

The trial was expected to recruit 338 patients in order to detect a 15% improvement in 3-year DFS; however, the safety monitoring committee stopped the trial early due to significant improvement in the observed DFS. Thus, the intent-to-treat analysis was conducted on 262 patients, with 131 patients in the chemotherapy arm and 131 in the surveillance one. The majority of patients enrolled had pT3 disease (30% pT2 and 65% pT3) and were node negative following lymph node dissection (91%). Noteworthy, of the patients receiving adjuvant chemotherapy, 66% were treated with gem–cis, and 68% successfully completed the four planned chemotherapy cycles. Approximately 50% of the patients undergoing chemotherapy developed a Grade 3 or greater adverse event, with only one patient suffering a death related to an upper gastrointestinal bleed.

Results

The POUT trial met its primary end point: a significant improvement in DFS (hazard ratio [HR]: 0.49 [confidence interval (CI): 0.31–0.76], $P = 0.001$) was observed at a median follow-up of 17.3 months. Following adjustment for nodal involvement, the difference was more pronounced with an HR of 0.47 (CI: 0.30–0.74), $P = 0.001$. On univariable analyses, positive margins and receipt of gem–carboplatin were not associated with an improved DFS following chemotherapy, which may be related to the short follow-up and the low sample size, but still questioning the potential benefit of a noncisplatin (i.e., carboplatin) regimen. On secondary end points, adjuvant chemotherapy was also associated with an improvement in RFS (HR: 0.49 [CI: 0.30–0.78], $P = 0.02$). A difference in the OS curves favored the adjuvant chemotherapy arm, but the difference remained nonsignificant likely due to the short follow-up.

Conclusion

In summary, the POUT trial provides exciting and convincing Level I evidence on the benefit associated with adjuvant chemotherapy administration in patients with locally invasive or node-positive UTUC. The unanswered questions are the potential benefit of noncisplatin-based chemotherapy regimens (thus questioning the even more strong rationale for neoadjuvant chemotherapy in the setting of UTUC where the radical surgery inevitably affects renal function),[3] the consistency of the benefit among subgroups (pN0/pN+, positive margins,…), and the benefit of adjuvant chemotherapy over chemotherapy at the time of relapse.[4] The latter is of importance, as in muscle-invasive bladder cancer, adjuvant chemotherapy failed to demonstrate a significant improvement in OS compared to delayed chemotherapy at the time of relapse (EORTC trial 30994), although lack of power, as a result of low accrual, might have impacted the outcomes.[4] Finally, the immunotherapy revolution that is ongoing in ulcerative colitis (UC) will likely impact the management of patients with UTUC. To date, clinical trials are ongoing in the adjuvant setting of UC that are including UTUC patients to receive either atezolizumab (NCT02450331) or nivolumab (NCT02632409), whereas no studies of preoperative immunotherapy are available to date. The opportunity to address clinical trials in the selected UTUC population is rationale, is feasible (thanks to the Institute of Cancer Research, United Kingdom), and is supported by different underlying biology in UTUC compared to UC originating from the bladder. Such differences may be mirrored by the mechanisms of response and resistance development to immune checkpoint inhibitor therapy.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Nephrometry Scoring System Selects Candidates for Radical Nephrectomy versus Nephron-Sparing Surgery for Treatment of Renal Masses and Predicts Surgical and Oncological Outcome

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Abstract

Purpose: The study was designed to ensure the sensitivity of preoperative planning by applying radius, endophytic/exophytic, nearness to collecting system, anterior/posterior, and location to poles (RENAL) nephrometry scoring system on computed tomography films of patients having organ-confined solid and cystic renal tumors and to assess its correlation with the surgical technique by applying RENAL on the specimen intraoperative. **Materials and Methods:** Eighty-five patients with organ-confined solid and cystic renal masses underwent RENAL nephrometry system which was correlated with the surgical technique either radical or nephron-sparing surgery or the surgical and oncological outcome. **Results:** RENAL nephrometry scoring system shows high sensitivity with the type and outcome of surgery of resection of the renal tumors. **Conclusion:** RENAL nephrometry score system is an objective method to help in the decision of surgical approach to resect organ-confined solid and cystic renal tumors.

Keywords: *Radius, endophytic/exophytic, nearness to collecting system, anterior/posterior, and location to poles system, nephron sparing, radical*

Introduction

Prevalence of renal masses increased due to advances of imaging modalities, so the classic triad of pain, hematuria, and palpable renal mass is not present except in advanced cases.[1]

There are multiple options for managing renal masses, particularly for those with small renal mass. Surgery is the gold standard for the treatment of localized renal cell carcinoma (RCC).[2-6]

Nephron-sparing surgery has become an established treatment for renal tumors, particularly when the preservation of renal parenchyma is critical as in single functioning kidney and bilateral synchronous pathology.[2,3]

Treatment of renal tumors depends on description of tumor anatomy and the experience of the surgeon. Hence, Alexander Kutikov and Uzzo have described the radius, endophytic/exophytic, nearness to collecting system, anterior/posterior, and location to poles (RENAL) nephrometry score in 2009.[7]

RENAL nephrometry score which was one of the first systems created to provide a standardized descriptive system for renal masses based on radiologic findings.

Target of these nephrometry scoring systems was to make comparative studies between operative results and give standard anatomical data of the tumor.[7-9]

This system could be reliable as it describes the tumor anatomical features as radius, exophytic/endophytic, nearness of the tumor the collecting system, location of the tumor to renal poles, and being anterior or posterior.[7]

Application of RENAL nephrometry scoring preoperatively may be used as a guide to the complexity and choice of surgery for solid and cystic renal masses and patient counseling, with reference to postoperative outcomes. Widespread use of this score may act as communication tools among specialists.[10-13]

Materials and Methods

Studying data of 85 patients who are fit for anesthesia and having resectable

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nonmetastatic solid and cystic renal tumors was done during the period of January 2018–April 2019.

Routine preoperative assessment of the patients included computed tomography (CT) scan with intravenous contrast.

RENAL system was applied on mass lesions in CT preoperatively and on the excised specimens postoperatively as follows:

Radius: one point is given to tumors that are ≤4 cm, two points are given to those that more than 4 cm not exceeding 7 cm, and those that measure 7 cm and more are given 3 points.

The relationship between the renal tumor and the surface of the renal cortex is described by exophytic/endophytic component.

Not all renal tumors are spherical, so the safest way to calculate this score is by imagination of where the renal cortex would normally be if the mass is not present as renal tumors distort the normal contour of the kidney.

The distance between tumor's outermost point and renal cortex <1> and the distance between tumor's most endophytic point and renal cortex <2> are measured.

If <1> is greater than <2>, so the tumor is exophytic and vice versa.

One point is given for masses that are 50% exophytic or more. Two points are given for those that are <50% exophytic. Three points are given for the totally submitted in the renal parenchyma.

The nearness of tumor's innermost point and the closest fat sinus or collecting system is checked in secretory phase CT.

Tumors 7 mm or more from the collecting system or renal fat sinus are given one point. Two points are given to those that are >4 mm but <7 mm away. Three points are given for <4 mm from the nearest collecting system or fat sinus.

The anterior tumors are assigned "a," while the posterior ones are assigned "p." Using axial CT aims to detect whether the renal tumor is anterior or posterior by drawing an imaginary line parallel to the direction of the renal hilar structures equally dividing the renal parenchyma into anterior and posterior planes.

The location component describes the relation of the tumor to the renal polar line which is an imaginary plane where the medial renal parenchyma first intersected with the renal sinus fat, collecting system, or vessels, especially in coronal CT.

One point is given for tumors that are completely above or below the polar lines.

Two points are given for those that are crossing <50%.

Three points are given for those that are completely between polar lines or cross-polar lines >50% of the tumor's radius.

When the tumor is hilar, "h" is added to the score giving it more complexity.

RENAL system is subdivided according to the complexity into low,[4-6] moderate,[7-9] and high.[10-12]

Results

Eighty-five patients were included in this study and subdivided according to the type of surgery into radical cases and nephron-sparing cases.

Table 1: Intra- and postoperative data among radical cases

	Mean±SD	Minimum	Maximum
Operative time	4.52±0.89	3.00	7.0
Average blood loss	362.30±198.46	100.00	1000.0
Blood loss in drain	252.46±172.34	100.00	1000.0
Postnephrometry score	10.43±1.07	7.00	12.0
Post-serum creatinine	1.37±0.74	0.40	6.0
Posthemoglobin	10.35±1.47	7.00	14.0
Safety margin (%)			
Free		58 (95.1)	
Not free		3 (4.9)	
Post urine leakage (%)			
Yes		0 (0.0)	
No		61 (100.0)	
Re intervention (%)			
Yes		3 (4.9)	
No		58 (95.1)	
Recurrence (%)			
Yes		0 (0.0)	
No		61 (100.0)	

SD: Standard deviation

Table 2: Intra- and postoperative data among nephron-sparing surgery cases

	Mean±SD	Minimum	Maximum
Operative time	5.29±1.09	3.00	7.00
Average blood loss	506.25±320.43	100.00	1500.00
Blood loss in drain	458.33±233.90	100.00	1000.00
Nephrometry score	6.96±1.82	4.00	9.00
Creatinine	1.90±0.93	1.00	5.00
Hemoglobin	10.29±1.44	8.00	12.70
Safety margin (%)			
Free		22 (84.61)	
Not free		4 (15.38)	
Urine leakage (%)			
Yes		8 (30.76)	
No		18 (69.23)	
Reintervention (%)			
Yes		3 (11.53)	
No		23 (88.46)	
Recurrence (%)			
Yes		0 (0.0)	
No		26 (100.0)	

SD: Standard deviation

The mean age among radical nephrectomy cases was 57.9 ± 13.4 years, while the mean body mass index (BMI) was 24.4 ± 1.6, with males representing 57.4% of cases [Figure 1].

The mean operative time was 4.52 h, average blood loss: 362.30 cc, blood loss in the drain: 252.46 cc, and application of the score on specimens with a mean score 10.43; three patients were complicated with not free safety margins and needed intervention.

Change in hemoglobin, creatinine, and nephrometry score after operation among radical cases

Forty-six cases showed no change in score comparing the application of the study on CT and specimens, while 15 showed up the score.

Personal data among (nephron-sparing surgery) cases

The mean age among (nephron-sparing surgery [NSS]) cases was 57.5 ± 10.8 years, while the mean BMI was 24.6 ± 1.8, with males representing 62.5% of the cases.

The mean operative time was 5.29 h, average blood loss was 506.25 cc, average blood loss in drain was 458.33 cc, and mean score was 6.96; four cases were complicated with not free safety margins and eight with urine leak from which three required intervention. No recurrences were detected.

Twenty-seven patients (31.7%) of the total 85 patients with moderate complexity nephrometry score were studied as follows:

Only one case (1.1%) of score 7 who underwent NSS was complicated with transient creatinine rise, 4 cases (4.7%) of score 8 were complicated with bleeding and the

Table 3: Comparison between the two study groups in preoperative data

	Type of surgery, mean±SD		*P*	Significant
	Radical	Partial		
Hemoglobin	11.56±1.86	12.39±1.54	0.057	NS
Creatinine	1.07±0.34	1.09±0.43	0.772	NS
Nephrometry score	10.21±1.07	6.92±1.82	0.001	HS
Complexity (%)				
Mild	0 (0.0)	10 (38.4)	0.001	HS
Moderate	11 (19.2)	16 (61.5)		
High	46 (80.7)	0 (0.0)		

NS: Not significant, HS: Highly significant, SD: Standard deviation

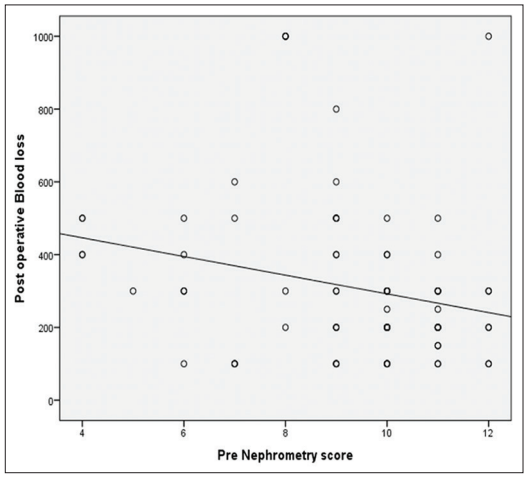

Figure 1: Post operative blood loss v/s pre nephrometry score

Table 4: Comparison between the two groups *in intra* and postoperative data

	Type of surgery, mean±SD		*P*	Significant
	Radical	Partial		
Operative time	4.52±0.89	5.29±1.09	0.001	HS
Average blood loss	362.30±198.46	506.25±320.43	0.014	S
Blood loss in drain	252.46±172.34	458.33±233.90	0.001	HS
Nephrometry score	10.43±1.07	6.96±1.82	0.001	HS
Hemoglobin	10.35±1.47	10.29±1.44	0.854	NS
Postserum creainine	1.37±0.74	1.90±0.93	0.007	HS
Safety margin (%)				
Free	58 (95.1)	20 (83.3)	0.09	NS
Not free	3 (4.9)	4 (16.7)		
Post urine leakage (%)				
Yes	0 (0.0)	8 (33.3)	0.001	HS
No	61 (100.0)	16 (66.7)		
Re intervention (%)				
Yes	3 (4.9)	3 (11.53)	0.34	NS
No	58 (95.1)	23 (88.46)		
Recurrence (%)				
Yes	0 (.0)	0 (0.0)	-	-
No	61 (100.0)	26 (100.0)		

NS: Not significant, HS: Highly significant, SD: Standard deviation

Table 5: Comparison between the two groups in change in hemoglobin, creatinine, and nephrometry score postoperatively

	Type of surgery				*P*	Significant
	Radical		Partial			
	Mean±SD	Median	Mean±SD	Median		
Hemoglobin change	1.21 (1.99	1 (0-2.5)	2.10 (2.22	2 (0-3)	0.125	NS
Hemoglobin % change	8.91 (15.46	9.1 (0-20)	15.67 (15.77	16.6 (0-27.3)	0.129	NS
Creatinine change	0.30 (0.73	0.2 (-0.1-0.5)	0.80 (0.95	0.4 (0.3-1)	0.001	HS
Creatinine % change	39.29 (77.89	20.3 (-8.3-50)	103.35 (162.15	50 (23.6-100)	0.005	HS
Change in nephrometry						
No change	46 (75.4)		25 (96.15)		0.03	S
Increased	15 (24.6)		1 (3.84)			

NS: Not significant, HS: Highly significant, SD: Standard deviation

Table 6: Relationship between the nephrometry score and the complications

Nephrometry score	4	5	6	7	8	9	10	11	12
Number of cases (%)	4 (4.7)	1 (1.1)	5 (5.88)	5 (5.88)	5 (5.88)	17 (20)	25 (29.41)	16 (18.82)	7 (8.23)
Type of surgery	4 NSS	1 NSS	5 NSS	5 NSS	4 NSS	7 NSS	25 Rad	16 Rad	7 Rad
Rad	4.7%	1.1%	5.88%	5.88%	1 Rad	10 Rad	29.41%	18.82%	8.23%
Nephron sparing (NSS)					4.7% NSS 1.1% Rad	8.23% NSS 11.7% Rad			
Complications	No	No	No	1 transient rise in creatinine	4 bleeding and urine leak with NSS	3 bleeding	No	No	3not free margin
	0%	0%	0%	1.1%	4.7%	3.52% and 4 not free margin and urine leak 4.7% with NSS	0%	0%	3.52%

NSS: Nephron-sparing surgery, Rad: Radical

safety margins were not free from malignant cells, and 7 cases (8.4%) of score 9 were complicated with bleeding and the safety margins were not free from malignant cells [Tables 1-6].

Discussion

In Kutikov and Uzzo study in 2009, 50 patients with solid renal tumors were subdivided into low and moderate, by which these two groups were treated with minimally invasive NSSs.

High complexity masses were treated with open partial or laparoscopic radical nephrectomy.[7]

In our study, all patients of low score underwent NSS, 48.25% of moderate score underwent NSS, while 51.72% of moderate score and all patients of high score underwent radical nephrectomy.

Patients' number in Kutikov's study was 50 patients, while in ours, it was 85, 80 of them underwent open surgery and five treated laparoscopically, while in Kutikov's study, 31 underwent laparoscopy (14 radical and 17 NSS) and 19 had open surgery (5 radical and 14 NSS).

Naya *et al*. studied 142 patients and found that the mean RENAL nephrometry score in the radical group was higher than that in the NSS (9 vs. 7; with $P < 0.0001$), which our study agrees with some studies.[14]

In 2013, Oh *et al*. studied that 206 patients underwent different approaches of surgeries.

Fifty-three underwent open radical nephrectomy, 83 laparoscopic radical nephrectomy, 31 open NSS, and 39 laparoscopic NSS.

The mean score in radical nephrectomy group was score 8.89 and for the NSS group, it was score 6.09), with $P < 0.0001$.[12]

In 2014, Cost *et al*. studied 65 patients, they classified renal masses into low, moderate, and high complexity groups, the same as in our study, two out of five of low score underwent radical nephrectomy, in contrast to our low score group who all underwent NSS, while three out of 48 patients in the high complexity group of Cost *et al*. underwent NSS, in contrast to our high complexity group who all underwent radical nephrectomy.[13]

Explanations for this are the difference between sample size and demographic characteristics and the different pathologies of the resected renal tumors, as 86.5% of the renal tumors in our study were RCC against only 16.4% in Cost's study.

Conclusion

RENAL scoring system is a good tool for making a decision for treating renal masses as follows:

Mild complexity group is better treated with NSS, score 7 moderate complexity renal tumors are more likely to be treated with NSS, while scores 8 and 9 are better treated with radical surgery, and high complexity group is better treated with radical surgery.

The RENAL nephrometry scoring system provides an easy methodology to stratify the complexity of renal tumors, aiding in treatment decision-making and counseling as well as providing a platform for standardized academic reporting. Although the data are preliminary, the nephrometry score appears to correlate with long-term outcomes. Renal abnormalities that might contribute to surgical morbidity, such as fusion or duplication, are not included in the scoring system, and as nephrometry becomes more widely adopted, modifications might become necessary. The interpreting radiologists will find that assigning a nephrometry score is simple and doing so will ensure that the salient features of a renal carcinoma are reported for operative planning.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Our Experience in the Treatment of Grade 4 Renal Injuries

Abstract

Introduction: The aim of this study is to evaluate treatment modalities in patients with Grade 4 renal injury. **Materials and Methods:** In this retrospective study, we included a total of 64 patients who were diagnosed with Grade 4 renal injury at our trauma center hospital from 2015 to 2019. Patients who underwent immediate laparotomy due to concomitant injuries or penetrating wounds were excluded from the study. Hemodynamic instability was the absolute indication for nephrectomy as well as failure to respond to conservative treatment. **Results:** In our study, 10 patients (15.6%) underwent immediate nephrectomy due to hemodynamic instability. In 15 out of 54 remaining patients, arterial embolization was performed. Twelve patients presented with urinoma which required intervention. In this subgroup of patients, a double J stent was inserted in four of the patients and a nephrostomy tube was placed in the remaining eight patients for perinephric space drainage. Nephrectomy was performed in four of the patients in the urinoma group. From the patients treated totally conservative, two presented with perirenal abscess, but only one underwent computed tomography-guided abscess drainage. **Conclusion:** Patients with Grade 4 renal injuries may be treated conservatively or in a minimally invasive way, and immediate nephrectomy should be performed only in case of hemodynamic instability.

Keywords: *Conservative management, Grade 4 renal injuries, renal trauma*

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Introduction

Renal injuries are a major cause of admission to urological clinics, and their treatment is often a challenge. The kidney is the third most common organ that is affected by multitraumatic injury after the spleen and the liver.[1] These injuries are mainly attributable to young people, with an average age of 31 years, and the vast majority is due to road accidents (63%).

Assessment of the overall renal injury severity is classified according to the American Association for the Surgery of Trauma (AAST) grading scale. This classification is based on the degree of renal parenchyma and blood vessel rupture and the extent of the subcapsular or perirenal hemorrhage [Figure 1 and Table 1].[2] Grade 4 injuries account for 19% of the total of renal injuries.[3] Since invasive radiology and endourology have allowed conservative treatment of such lesions either by arterial embolization or double J stent or nephrostomy insertion, urologists nowadays have many options apart from radical nephrectomy in the treatment of Grade 4 trauma, and in most cases, the organ may be preserved.[4] In this study, we present our departments' experience in the treatment of Grade 4 renal trauma focusing on totally conservative or minimally invasive modalities based on incidents that occurred at our trauma center hospital between 2015 and 2019.

Materials and Methods

In this retrospective study, we collected data from a total of 64 trauma patients diagnosed with Grade 4 renal injury in our department from 2015 to 2019. Diagnosis was based on CT scan which was performed in all patients. All patients with renal trauma due to penetrating organs were excluded from the study. Patients who underwent immediate laparotomy due to concomitant injuries were also excluded. Absolute indication for immediate nephrectomy was hemodynamic instability. All hemodynamic stable patients were treated conservatively with blood transfusions if necessary, and a minimally invasive approach with arterial embolization was performed in patients with continuous renal bleeding. Grade 4 renal injuries also include patients with trauma to the renal collective system with

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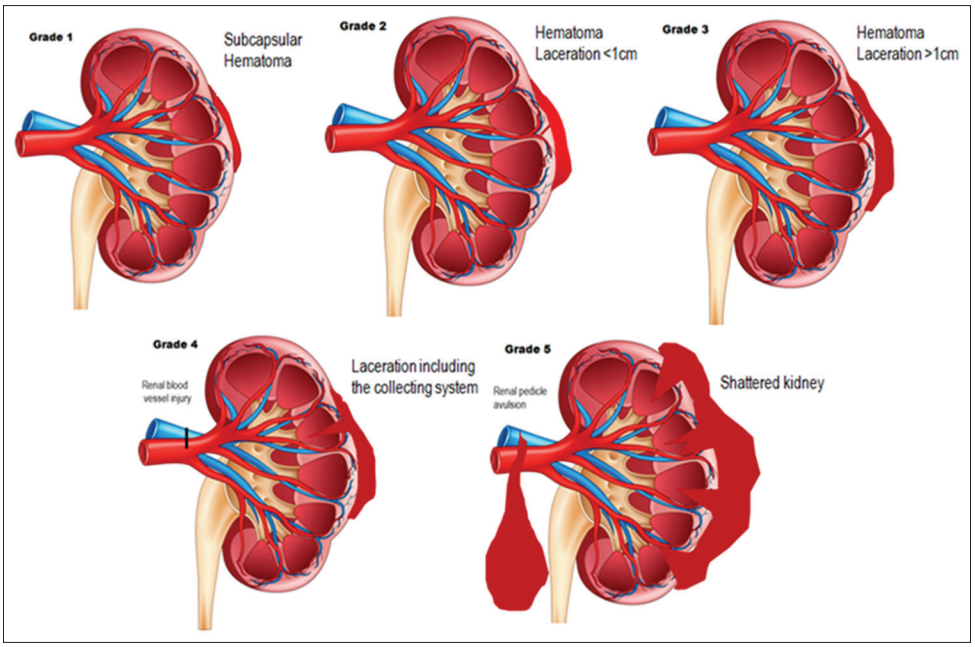

Figure 1: American Association for the Surgery of Trauma kidney injury scale (published under license by freepick.com)

Table 1: American Association for the Surgery of Trauma kidney injury scale

Grade	Description of injury
1	Contusion or nonexpanding subcapsular hematoma No laceration
2	Nonexpanding perirenal hematoma Cortical laceration <1 cm deep without extravasation
3	Cortical laceration >1 cm without urinary extravasation
4	Parenchymal laceration: through corticomedullary junction into collecting system or Vascular: segmental renal artery or vein injury with contained hematoma, or partial vessel laceration, or vessel thrombosis
5	Parenchymal: shattered kidney or Vascular: renal pedicle or avulsion

*Advance one grade for bilateral injuries up to Grade III.
AAST: American Association for the Surgery of Trauma

subsequent urine leak and urinoma formation. A double J stent was not inserted in all patients with urine leak but only in patients with severe urinoma or fever. Decision was based on the urologist experience in the management of such trauma. In cases of large perirenal urinoma or abscess, a nephrostomy tube was inserted.

Results

A total of 64 patients diagnosed with Grade 4 renal trauma were treated in our department between 2015 and 2019. All patients managed to undergo computed tomography (CT) scan in the emergency department, and patients with severe hemodynamic instability requiring immediate surgical exploration were excluded from the study. Vital signs were recorded throughout the initial evaluation giving the most reliable indication of the urgency of the situation as immediate nephrectomy should be performed only in patients with hemodynamic instability. The median age was 34 years, and most patients were males (58 males, 6 females). The most common cause was road accident (50 patients), followed by falls (10 patients) and work accidents (4 patients). The left kidney was most usually injured (40 patients), and visible hematuria was present in 32 patients. Concomitant injuries not requiring surgical interventions were present in 48 patients including fractured ribs, splenic trauma, or liver trauma.

As far as it concerns trauma management, 10 patients (15.6%) underwent immediate nephrectomy due to hemodynamic instability after the diagnosis of a Grade 4 renal injury. From the remaining 54 patients, 15 (23.4%) presented continuous renal bleeding, and an arterial embolization was performed. All patients were stable after the embolization, and no further embolization or surgical exploration was necessary. In addition, a double J stent was inserted in 4 (6.3%) patients due to severe urine leak, and a nephrostomy tube was placed in 8 (12.5%) patients in order to drain severe urinoma. During hospitalization, an abscess was diagnosed in 2 patients, but only in one, drainage was performed under CT guidance.

Discussion

Renal injury is characterized as blunt (90%), or acute penetrating (10%), depending on the mechanism of injury and the type of renal damage. Assessment of the overall renal injury severity is classified according to the AAST grading scale. This classification is based on the degree of renal parenchymal and blood vessel rupture and the

extent of the subcapsular or perirenal hemorrhage. Grade 4 traumas are diagnosed in cases of either parenchymal laceration through the corticomedullary junction into the collecting system or in cases of vascular trauma involving segmental renal artery or vein injury with contained hematoma, or partial vessel laceration, or vessel thrombosis.[2] Grade 4 injuries account for 19% of the total of renal injuries.[3] The absolute indication of immediate surgical exploration and nephrectomy if necessary is the hemodynamic instability regardless of the grade of injury.[5] As a result, Grade 1–3 renal injuries are treated in a preservative way, and in Grade 4 patients, the approach should be individualized.[4,6] As far as it concerns Grade 5 renal injury, surgical exploration is usually mandatory, although in some trauma centers with experience in renal injuries, an initial conservative approach may be applied, provided that the patient is hemodynamically stable.[7,8]

As far as it concerns acute penetrating traumas (stab wounds and gunshot wounds), in the past years, the recommendation was in favor of surgical exploration and subsequent nephrectomy when necessary. Nowadays, based on modern imaging techniques and growing experience in the conservative management of renal trauma, the trend is toward a more conservative approach even in penetrating trauma. Thus, nephrectomy is only recommended for wounds from high-velocity gun bullets that cause extensive damage.[9,10] We must also underline that whenever surgical exploration is performed either for blunt or penetrating renal trauma, if the bleeding can be controlled and sufficient renal tissue is present, efforts should be made to preserve the kidney.[11]

In Buckley's *et al*. study, 153 Grade 4 renal lesions were studied, of which 43 were cases in which there was isolated kidney injury without concomitant injury. In this study, 25 (58%) of these patients were initially treated conservatively, and eventually, 22 (88%) maintained their kidneys. The remaining 18 patients underwent surgical exploration and 15 managed to retain their kidneys.[9] Moreover, Santucci and McAninch have evaluated the management of 2047 patients with Grade 4 kidney injury. The kidney was retained in 91% of the cases, while 22% of the patients were treated totally conservatively.[12] In another study by Kuo *et al*. involving 95 patients, the kidney was preserved in 75% of the cases.[13] In a similar study by Wright *et al*., a rate of 77.6% of kidney preservation in such injuries was reported.[14]

Conservative management of hemodynamic stable patients with Grade 4 renal trauma is not without complications. Early complications include bleeding, infection, abscess formation, and urinary extravasation with urinoma formation. Bleeding is a major complication which often is life-threatening and should be managed by arterial embolization.[15] As far as it concerns the formation of urinoma, it can also be managed in a minimally invasive way by ureteral stent or nephrostomy placement.[16]

Conclusion

Grade 4 renal trauma can be treated conservatively in most cases. In cases of continuous bleeding, arterial embolization must be performed, and in cases of urinoma, a ureteral stent or a nephrostomy tube may be placed. Absolute indication for surgical intervention and nephrectomy if necessary is hemodynamic instability, failure of conservative or minimally invasive efforts, or laparotomy for concomitant injuries. As a result, surgical exploration is limited to a minority of cases with Grade 4 renal trauma.

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Conflicts of interest

There are no conflicts of interest.

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Review

Use of Carbohydrate Antigen 19-9 in the Management of Bladder Cancer

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Abstract

Over the years, a distant effort has been made to find new prognostic biomarkers in the assessment of accurate response to treatment and detection of recurrences of bladder cancer. Among them, the carbohydrate-rich glycoprotein, Carbohydrate Antigen (CA) 19-9 has shown some usefulness as it is linked with the tumour aggressiveness and the prognosis of disease. Aim of this study is to review available evidence about the role of CA 19-9 in diagnosis, staging and prognosis of bladder cancer. After careful review of the related articles, a total of 16 useful and valued studies were found on the database. These studies evaluated relation of CA 19-9 to various different aspects of bladder cancer. These aspects include use of CA 19-9 as a tool for detection of bladder cancer, its role in the assessment of the prognosis at diagnosis and also looked at the significance of the CA 19-9 in the response to treatment of bladder cancer. These studies indicate that CA19-9 sensitivity and specificity was 71.6 and 91.6 in high-grade tumour and sensitivity of 74% and 83% in Ta and T1 tumours. Serum levels of > 29 U/ml are associated with shorter survival time and carried a 2.54 higher risk of death. High levels in metastatic disease are associated with increase response to chemotherapy. Although these results are encouraging, but due to the limited evidence, there can be no strong recommendation for use of the biomarker CA 19-9 and further studies are needed to establish a useful link.

Keywords: *Bladder cancer, carbohydrate antigen 19-9, systematic review*

Introduction

Bladder cancer (BC) is the 11th most common cancer in the general population of Europe, with worldwide age-standardized mortality rate estimate of 3.2 for men and 0.9 for women, respectively.[1] Smoking tobacco, increased age, and industrial chemical exposure are all considered major risk factors for the development of this disease.[2] Among patients diagnosed with BC, approximately two-thirds present with non-invasive tumors (carcinoma *in situ*, state Ta-T1). The rest of patients present with T2-T4 tumors and are exposed to a higher risk of cancer-specific mortality.[3]

Radical cystectomy (RC) accompanied with neoadjuvant chemotherapy (NAC) is considered the best option for definitive treatment, although bladder-sparing approaches may also offer comparable results.[4] Ultimately, almost half of the patients after RC present with localized recurrences and distant metastases, impoverishing dramatically the prognosis of patients with BC.[3] In this regard, over the years, a distant effort by researchers has been made to provide new prognostic biomarkers in the assessment of accurate response to treatment and prompt detection of recurrences.

Among several markers, the carbohydrate-rich glycoprotein, carbohydrate antigen (CA) 19-9, has shown some usefulness as it is linked with the tumor aggressiveness and the prognosis of the disease.[5,6] Moreover, other authors concluded that this marker might predict the effect of treatments in patients with advanced urothelial carcinoma.[7] In this study, we revisited the literature reviewing the possible role of CA 19-9 in the management of BC.

Materials and Methods

The systematic review was performed according to the Cochrane reviews guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We searched PubMed, Embase, and Cochrane Library from inception to August 2019, and all English-language articles were included in the original search. The search terms included "Bladder cancer," "Urothelial cancer," "Carbohydrate antigen 19-9," and "CA 19-9." Boolean operators (AND, OR)

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were used with the above search terms to refine the search.

We included all studies of patients with BC, with CA 19-9 measurements. We also looked into available case series of nonurothelial malignancies such as colorectal malignancy and benign urological diseases where CA 19-9 was measured.

Results

Literature search and included studies

After an initial search, 16 articles (2016 patients) met the inclusion criteria for the final review with the first paper published in 1996. We also reviewed twelve other studies including case series, to explain the established role of CA 19-9 in other conditions.

Patient characteristics

There were 2016 patients with a median age of 69 years. All patients had a diagnosis of BC and CA 19-9 level reported [Table 1].

Established clinical role of carbohydrate antigen 19-9

CA 19-9 is a monosialoganglioside attached to sialylated Lewis A blood group antigen and circulates in serum with a half-life of approximately 14 h. This glycoprotein is produced by pancreatic and biliary epithelium and secreted by gastric, colonic, endometrial, and salivary epithelia.[8] Since the marker is considered tumor-associated rather than tumor-specific, increased blood levels of CA 19-9 should be interpreted wisely. Cholangitis and other benign diseases such as cholestasis may also increase the blood levels of the marker and makes it difficult to differentiate between malignant and benign conditions. This is important for gastroenterology cases as only those patients with a suspicious pancreatic mass and increased blood levels of CA 19-9 should be considered as having a pancreatic adenocarcinoma and treated so.[8] In case where a diagnosis of pancreatic carcinomas has been established, preoperative CA 19-9 levels can add useful information regarding staging and prognosis, whereas normalization or a decline of serum CA 19-9 after treatment is linked with better response and improved survival.[9] As far as the urinary tract is concerned, cancer cells of conventional transitional cell carcinoma or mixed with other infrequent subtypes have been reported as a bed for expression of CA 19-9 in their surface.[10-13] Therefore, several studies have been conducted searching for the possible role of the biomarker in the diagnosis and the assessment of the severity of the disease.

Table 1: Patients Characteristics in studies analyzed for systematic review

Authors	Year published	Journal	Review period	Median age	Patients number
Pectasides, D. Bafaloucos, D. Antoniou	1996	American Journal of Clinical Oncology	1990-1993	67 years	76
Else Marie Vestergaard, Hans Wolf, and Torben F. Ørntoft	1998	Clinical Chemistry	-	70 (men) 67 (women)	81
AM Cook, RA Huddart, G Jay, A Norman, DP Dearnaley and A Horwich	2000	British Journal of Cancer	1992-1997	-	74
Kazuhiko Sashide Hideyuki Isobe Yoshiaki Wakumoto	2004	Urologia Internationalis	1992-1996	64.3	164
David Margel, Raanan Tal and Jack Baniel	2007	The Journal of Urology	1999-2004	69	91
Keiji Nagao, Yukio Itoh, Kazuhiko Fujita and Makoto Fujime	2007	International Journal of Urology	…….	59.5	121
David Margel, Amir Harel, Ofer Yossepowitch, and Jack Baniel	2009	American Cancer Society	1999-2007	69	133
Axel Hegele, Verena Mecklenburg, Zoltan Varga	2010	Anticancer Research	2008-2010	70	231
Keya Pal, Suparna Roy, Samim Ali Mondal	2011	Urology Journal	18 months	58.7	47
Dipendra Kumar Jha, Ankush Mittal, Satrudhan Pd Gupta	2013	Asian Pacific Journal of Cancer Prevention	July 2012-December 2012 (6 months)	……	15
Suparna Roy, Anindya Dasgupta, Kaushik Kar	2013	Int Braz J Urol	2008-2010	….	55
Hamed Ahmadi, Hooman Djaladat, Jie Cai	2014	Urologic Oncology	2004-2009	69	186
Minekatsu Taga, Hitomi Hoshino, Shulin Low	2015	Urologic Oncology		72.1	78
Qing-hai Wang, Zhi-gang Ji, Zhi-gang Chen	2015	International Journal of Surgery	5 years	72	144
X oroush T. Bazargani, homas G. Clifford, ooman Djaladat	2019	Urologic Oncology	2011-2016	71	480
Yaegashi H. Izumi K, Kadomoto S	2019	International Institute of Anticancer Research	2008-2014	…….	40

Use of carbohydrate antigen 19-9 as a tool for the detection of bladder cancer

About three decades ago, Tizzani *et al*. investigated the diagnostic role of three tumor markers, including CA 19-9, by measuring their urinary levels in patients with BC.[14] The authors observed that CA 19-9 urinary levels were high in patients with urothelial cancer. The other important observation was that the levels were higher in high-grade tumors as compared to low-grade tumors. In general, the marker offered adequate sensitivity and specificity of 71.6% and 91.6%, respectively.[14] Similarly, Casetta *et al*. have reported that the combination of CA 19-9 with tissue polypeptide antigen demonstrated a sensitivity of 74% and 83% in Ta and T1 tumors, respectively, and 62% in well-differentiated tumors.[6] In another study, Vestergaard *et al*. observed that urinary levels of CA 19-9 were significantly higher in patients with BC than healthy individuals, whereas the highest levels were observed in cases of concomitant dysplasia of the urothelium. However, the authors raised the concern about the complexity of the synthesis of CA 19-9 and pointed out those results may vary according to genetic differences among individuals.[15] Nagao *et al*. observed that urinary levels of the biomarker CA19-9 achieved a similar detection rate of high-grade bladder tumors when compared to urinary cytology. The Marker also showed some encouraging results in detecting low-grade bladder cancers.[16] The latter capacity of the marker was also highlighted from Pal *et al*., who observed that urinary CA 19-9 levels could predict low-grade tumors more efficiently than urinary cytology and was not affected by the presence of hemoglobin.[17] Likewise, Roy *et al*. reported that increased urinary levels of the biomarkers indicated the presence of the low-grade carcinoma of the bladder, drawing attention to the superiority of CA 19-9 in comparison to urinary cytology in the same patients.[18] Finally, in a delicate, experimental study, Escorcia *et al*. used a CA19.9-specific antibody-based construct for positron emission tomography for the detection of urothelial cancer in the bladder of mice and reported remarkably promising results.[19]

Role of carbohydrate antigen 19-9 in the assessment of the prognosis at diagnosis

Commonly reported by most studies, the level of the CA 19-9 is associated with the advanced stage and bulkiness of the tumor, which proportionally is associated with the prognosis of the condition. Sashide *et al*. concluded that CA 19-9 was strongly associated with the high stage, tumor bulk, poor prognosis, and reduced survival at the time of the diagnosis.[5] Furthermore, Casetta *et al*. reported that pre-operative, urinary levels of CA 19-9 >300 U/ml in patients with infiltrating disease were strongly associated with poor prognosis.[6] Furthermore, Margel *et al*. observed that patients with clinically organ confined disease (cT2 or less N0) and high precystectomy levels of CA 19-9 had poor prognosis, highlighting the role of the biomarker as a possible independent predictor of disease specific mortality.[20] For the aforementioned, the same authors included CA 19-9 as an individual parameter in a nomogram for the prediction of nonconfined disease before cystectomy, in an effort to achieve a more accurate estimation of pathologic stage.[21] Furthermore, in another prospective study, the role of CA 19-9 as an independent prognostic factor of mortality in patients with BC was highlighted by the authors; patients with known BC and increased serum levels (>29 U/ml) experienced significantly shorter survival time and carried a 2.54 higher risk of death.[22]

Significance of the carbohydrate antigen 19-9 in the response of therapy

CA 19-9 may carry a significant role in making an accurate assessment to check the response of treatment. The normalization of serum levels of the biomarker is associated with success of treatment, whereas the fluctuation of serum levels of CA 19-9 indicates recurrence.[23] In a notable, recent study, Bazargani *et al*. reported that patients who had the biomarker normalized after NAC enjoyed a significant longer time to recurrence or progression and overall longer survival, whereas at the same time, the pathological stage did not differ between responders and non-responders.[24] In the framework of advanced disease, persistence or elevation of the marker indicated poor response in patients who either received NAC or chemotherapy due to metastatic disease of BC.[25] Moreover, in terms of advanced BC, CA 19-9 has also been used as part of a panel of biomarkers for the response in chemotherapy and data by Cook *et al*. showed that clinical response was accompanied with a response of at least one marker. If tumour markers show response to chemotherapy, it occurs very quickly in first eight weeks of treatment.[26] Finally, Yaegashi *et al*. reported that increased levels of serum CA 19-9 in patients with metastatic BC are associated with better response in chemotherapy, implicating that serum levels of the biomarker may act as markers of chemosensitivity.[7]

Discussion

The pursuit of reliable biomarkers in the management of BC is justified due to some reasons. First of all, in the setting of the diagnostic process and follow-up of non-muscle invasive tumors, cytology remains the only recommended marker, especially for the detection of high-grade tumors, but some limitations apply. The interpretation is user dependent, it is susceptible to false-positive results, and it lacks sensitivity in low-grade tumors.[1]

On the other hand, urinary levels of CA 19-9 seem to carry some significance for the detection of low-grade tumors in comparison to cytology and the modality looks promising.[17,18] However, it should be kept in mind that

urinary levels of the biomarker may be elevated in urinary tract obstruction, which could limit its role in some patients.[27] Furthermore, what really matters in patients with non-muscle invasive tumors is the grade, as this is the factor that dictates prognosis.[3]

If the modality should be combined with cytology in order to substitute or assist or avoid unnecessary cystoscopies for the diagnosis or follow-up of BC, it could be a matter of future, prospective studies. However, no evidence exists yet that the use of the marker can be recommended. Second, another common problem in BC is clinical under staging or over staging, which is addressed to low accuracy of staging modalities (bimanual examination, computed tomography, or magnetic resonance imaging).[3]

In previous studies, Margel *et al*. have demonstrated that increased serum levels of CA 19-9 in patients who underwent cystectomy for localized disease (T2N0M0) were at high risk of extravesical and nodal positive disease; the patients in that setting had inevitably reduced survival.[28] Although the patients in those cohorts did not receive NAC, data implicate that the biomarkers such as CA 19-9 might bridge the gap between clinical and pathological staging, avoiding unnecessary interventions and alternate management toward the most feasible outcome. Similarly, in an aforementioned study, patients who received NAC and had their biomarkers normalized enjoyed significantly longer overall survival and lower recurrence, although the pathological stage did not differ between responders and non-responders.[24] These results should be considered significant, as far as the biomarker might provide a way to unmask patients at highest risk and alternate the management of the condition for the benefit of these patients.

Under these circumstances, CA 19-9 could play a role in BC similar to that in pancreatic carcinoma; having a limited role in diagnosis and should the diagnosis of the urothelial carcinoma has been set, serum levels can be a measure of tumor aggressiveness and help in the monitoring of the disease.[29] However, pitfalls may occur as far as tumors poorly differentiated may not express CA 19-9, indicating an unpredictably high malignant potential.[30]

Conclusions and Main Points

To sum up:

- Results from studies are encouraging, but due to the limited evidence, there can be no strong recommendation for the use of the biomarker CA 19-9 as a tool in the diagnosis and follow-up of non-muscle invasive BC
- CA19-9 sensitivity and specificity were 71.6 and 91.6 in high-grade tumor and sensitivity of 74% and 83% in Ta and T1 tumors
- Serum levels of >29 U/ml are associated with shorter survival time and carried a 2.54 higher risk of death
- High levels in metastatic disease are associated with increase response to chemotherapy.

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Conflicts of interest

There are no conflicts of interest.

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Review

The Online Learning in Medical Education: A Novel Challenge in the Era of COVID-19 Pandemic

Abstract

Online learning has a well-established role in medical education, and it is well accepted by students. Electronic learning (e-learning) strategy is aimed at improving the quality of medical education by providing students with equal access to quality learning resources. The main advantages of online learning are its flexibility and the capacity for learning to be self-paced. Online learning may be particularly useful for under- and post-graduate medical education. Virtual lectures can substitute conventional lectures in medical education in multiple fields. Online learning has several barriers including lack of time and poor technical skills of their providers, inadequate infrastructure, and the absence of development strategies of the universities. The current COVID-19 pandemic may represent a real challenge to medical education. Online learning techniques can be used to complete the curricula for medical schools during this crisis. This review presents a robust evidence base for e-learning in medical education. Further, it compares online and offline learning methods in medical education.

Keywords: *Classroom learning, COVID-19, electronic learning, medical education, online learning, pandemic*

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Introduction

Community-based education of medical students has increased vastly.[1] Distance electronic learning (e-learning) refers to the use of technologies based on healthcare delivered on distance and covers areas, such as electronic health, tele-health, telematics, telemedicine, and tele-education. The traditional static concept of medical education can be changed with the help of the novel technologic revolution. Telemedicine is a term for distance medical procedure, of both diagnostic and therapeutic procedures supporting decision-making.[2] E-learning technologies offer learner control of the content and pace of the learning, allowing them to tailor their learning objectives. In diverse medical education contexts, e-learning appears to be at least as effective as traditional instructor-led methods, such as lectures at the auditorium. Students do not see e-learning as replacing traditional learning but as a complement to it.[3] Massive open online courses (MOOCs) are increasingly available in medicine. These MOOCs are offered through various scientific (commercial and noncommercial) online platforms. When offered through reputable institutions, they can provide valuable access to reliable information without constraints of time, geographical location, or level of education.[4] Computer-based teaching and learning are as effective as typical lecture-based teaching sessions for educating postgraduates.[5]

Several factors consist as barriers to online learning: administrative issues, social interaction, academic and technical skills, learner motivation, time and support for studies, and cost and access to the internet.[6] The first meta-analysis to assess the effect of internet-based instruction for healthcare professional (HCP) learners compared with noninternet interventions (offline learning) was conducted by Cook *et al*.[7] They concluded that the internet-based learning is associated with large positive effects compared with no intervention at all. Effects compared with noninternet instructional methods are heterogeneous and generally small, suggesting effectiveness similar to the traditional methods.[7] Richmond *et al*. conducted a meta-analysis and comprehensive review to compare online

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versus alternative methods for training licensed HCPs to deliver clinical interventions.[8] They concluded that online methods may be as effective as alternative methods for training HCPs in clinical interventions for the outcomes of knowledge and clinical behavior.[8]

Utilizing e-learning can result in greater educational opportunities for students while simultaneously enhancing faculty efficiency. However, this potential of e-learning assumes a certain level of institutional readiness in human and infrastructural resources that are not always present in low- and middle-income developing countries. Institutional adoption of e-learning ensures the alignment of new tools to the educational and economic context.[9]

The epidemic of the 2019 coronavirus disease (COVID-19) is caused by a novel virus first detected in Wuhan, China. This virus was previously named as 2019-nCoV. China officially declared the epidemic as an outbreak on January 20 when obvious human-to-human transmissions were ascertained with reagent probes and primers distributed to local agencies.[10] The COVID-19 outbreak has rapidly transitioned into a worldwide pandemic. This development has had serious implications for public institutions and raises particular questions for medical schools. A substantial number of medical students are in the process of preparing for or undertaking assessments that require clinical exposure. The effect of COVID-19 on medical education could, therefore, be considerable.[11]

This current review aims to present a robust evidence base for e-learning in medical education and specifically focus on the e-learning method for medical students and postgraduate doctors. We provide a review of the aims, barriers, and solutions to online learning. In addition, we compare online and offline learning methods in medical education. Furthermore, we present a brief review of COVID-19 disease and its effect on medical education and the place of online learning in these circumstances.

Aims of Online Learning in Medical Education

E-learning can be used to aid the teaching of physical skills. A video showing the technique and explaining the theory by putting it into context could prime learners before they attend the teaching session. One area that has generated interest in medical education is the "virtual patient," who helps teaching the skills of diagnosis and management through online interaction.[12] E-learning is a viable solution for medical educators faced with many challenges, including promoting self-directed learning, providing flexible learning opportunities that would offer continuous availability for learners, and engaging learners to augment continuous professional development.[13] Students rate e-learning just as highly as other traditional methods of clinical skills teaching and acknowledge its integration in a combined approach. Developers of clinical skills curricula need to ensure that e-learning environments utilize media that encourage deeper approaches to learn.[14]

Compared to conventional learning, e-learning has the advantage that participants can choose the place and time of education themselves. Within a clinical context, the effect of internet-based continuing medical education (CME) programs is comparable to traditional approaches of CME.[15] There are three e-learning modalities that promise great potential for innovative training in the future. These modalities include simulation technology, synchronous learning delivery, and web-based or videoconferencing for standardized patient-based training.[16] There are important implications, too, for globalization in medical education and for the continuity of education from undergraduate to postgraduate and continuing education.[17]

Virtual learning environments (VLEs) can be a compelling and powerful way to support and manage contemporary medical education. A VLE purposively aligned to a course can provide a central access point and reference mechanism for all course components.[18] The provision of e-learning tools or complex-blended learning scenarios depends on an online platform where students and teachers can get access. To address this issue, different forms of learning management systems (LMSs) have been established in medical faculties worldwide. An LMS can be defined as software that automates the administration, tracks all training events, and delivers learning contents rapidly.[19]

Barriers and Solutions of Online Learning in Medical Education

Many factors can influence whether or not an online learning program will succeed or fail, ranging from student-led factors to staff-led factors. Lack of skills, in particular, technical skills, was found to be one of the major barriers met by educators when engaging with the development and implementation of online learning. Medical educators are already under pressure to find sufficient time to manage teaching, research, and maintain a work–life balance. In this context, inadequate time can be a significant barrier. In many cases, the lack of infrastructure and technology can be seen as a barrier in medical education, typically in low–medium-income developing countries. The negative attitude among educators in engaging with new technologies is another barrier to the development and implementation of online learning.[20]

A two-round Delphi study, aiming to identify expectations and barriers to e-learning in primary healthcare education, has been published.[21] Results showed that there was a positive attitude to e-learning, but there was concern about the lack of orientation toward users' needs and the poor development of innovative didactical concepts. In implementing e-learning in primary care, education should be independent of financial influence from the healthcare industry to eliminate conflicts of interest.[21] According

to the study, adaptation to a new learning environment is necessary for virtual learning. Many barriers were found to self-directed learning in virtual education, including cognitive barriers (information overload and lack of focus on learning), communication barriers (inadequate coping skills and inadequate writing skills), and educational environment barriers (heavy workload and role ambiguity).[22] An MOOC experience of young family doctors has been published.[23] The limitation of course completion depended on internet connectivity and high English comprehension. First, a fast and reliable internet connection with appropriate bandwidth was needed to watch the videos. Without this, the content did not load properly and affected negatively the learning process. A second limitation was that the weekly modules and videos were in only English.[23] The key challenge is systematic and pedagogical approach to e-learning in which three equally important considerations must be balanced: organization, pedagogy, and technology.[24]

There are several critical success factors for e-learning programs. These include institutional characteristics: organizational support (time allocated for training); cultural support (supportive learning environment); and information technology support (including both technical infrastructure and learner technology assistance). Instructor and learners' characteristics include motivation, positive attitudes toward e-learning, and digital literacy.[25] Students of the online learning program often provide recommendations for strategies to address these issues, such as how to communicate, facilitate teamwork, and optimize time management.[26]

Online Learning for Medical Students and Fellows

Graduate students had a significantly more favorable assessment of the e-learning resources than their undergraduate colleagues. It should not be assumed that all students will choose to use an e-learning resource in the same way and instructional design should enable alternative approaches.[27] A study aiming to evaluate medical students' perception of the usefulness and effectiveness of e-learning was done.[28] Of the participants, 92% found it enjoyable and 95% found the e-learning package useful; 75% perceived it to be effective in increasing their performance; and 91% believed it increased their knowledge in consulting skills.[28]

Early reports in the literature describe using student-generated questions as a method of student learning as well as augmenting question examination banks. However, reports on the performance of student-generated versus faculty-generated questions remain limited. A study was implemented to compare the question performance of student-generated versus faculty-generated multiple-choice questions (MCQs). This study suggests that student-generated compared to faculty-generated MCQs have similar item discrimination scores but are perhaps more difficult questions.[29] There is a gap between medical faculty's positive perceptions of e-learning resources and their low use of such resources. The most frequently selected reasons for not using e-learning resources in faculty members of medical school teachers were the lack of resources relevant to lectures, lack of time to use those resources during lectures, and the unawareness of their availability for learning.[30] The Korean Consortium for E-Learning in Medical Education was formed for the collaboration in providing quality online learning resources for medical schools.[31] This e-learning strategy aimed at improving the quality of medical education at the national level by providing students with equal access to quality learning resources. The consortium also planned to share e-learning content with medical schools in other countries.[31]

Residency programs could be better resourced to integrate e-learning technologies. Asynchronous e-learning was used more than synchronous, mainly because of busy resident schedules and duty-hour restrictions. In a survey of residency program directors (RPDs), it was found that program directors' perceptions of e-learning were relatively moderate and future research should determine whether RPD reluctance to adopt e-learning was based on unawareness of the evidence, perceptions that e-learning is expensive, or judgments about value versus effectiveness.[32] Another survey was done to characterize the educational tools used by surgical residents. Respondents used online textbooks and journal articles most often to investigate timely patient care issues. In contrast, mobile platform applications and online videos/lectures were used least. Fewer than half of the respondents used simulators, limited by clinical duties, absence of feedback/supervision, and lack of working supplies. Simulators remain a required tool for laparoscopic training and incorporation of structured feedback.[33] A surgical postgraduate year (PGY)-1 "Boot Camp" as a preparatory simulation-based training was implemented at the onset of the internship. This orientation process included exposure to simulated patient care encounters and technical skills training essentials. Scientists propose the "Boot Camp" performance measures as parameters for assessment of resident training.[34]

Minimally invasive surgery is a particularly challenging competency training area, requiring significant allocation of resident and faculty time and resources. "Laparoscopy 101" is a resource for the training and assessment of competency residents in minimal invasive surgery. It consists of CD-ROM-based self-paced didactic self-instruction modules, skills laboratories, and web-based testing, evaluation, and reporting. The "Laparoscopy 101" curriculum is well accepted by trainees and yields significant improvement in PGY-2 minimally invasive surgery competencies.[35]

A study was carried out for comparative evaluation of case-based learning (CBL) aided with mobile phone

"WhatsApp" and didactic lectures while teaching a topic to the 2nd-year medical students. CBL aided by "WhatsApp" helped students acquire knowledge, discuss and learn actively, score more, and retain better than the standard lecture.[36] While didactic conferences are an important component of residency training, delivering them efficiently is a challenge for many programs, especially when residents are located in different places. E-conferences (virtual conference) proved to be an effective method of delivering didactics in the residency program. Its many advantages included ease of use, cost-efficiency, and wide availability of equipment.[37] Providing effective multisite didactic teaching in residency programs remains a challenge. In Wayne State University, a synchronous two-way audio and video internet-transmitted distance learning methodology in two sites has been introduced.[38] The didactic sessions were rated highly by both groups, with no significant differences in the resident satisfaction survey. The distance learning method was received positively by learners.[38]

The Area Health Education Centers Program at the University of Arkansas for Medical Sciences sought to deliver high-quality presentations to family practice residents at remote locations, using a two-way interactive video.[39] Four conferences were broadcast to five remote residency programs, and two local programs received identical conferences on-site. The negative attitude shift toward interactive video may have been because it was a new experience, or the preparation of the faculty was inadequate.[39] A study has been done to evaluate the educational effectiveness of a clinically integrated e-learning course for teaching basic evidence-based medicine (EBM) among postgraduate medical trainees compared to a traditional lecture-based course of equivalent content. A clinically integrated e-learning EBM course was compared to a lecture-based course among postgraduate trainees at the foundation or internship level in seven teaching hospitals in the United Kingdom (UK).[40] An e-learning course in EBM was as effective in improving knowledge as a standard lecture-based course. The benefits of an e-learning approach need to be considered when planning EBM curricula as it allows standardization of teaching materials and is a potentially cost-effective alternative to standard lecture-based teaching.[40]

Online Learning for Postgraduate Doctors

Postgraduate medical education involves the use of online learning tools. Online learning modules could have an important role in improving the clinical practice of newly qualified doctors. These modules or packages are the tools that consist of key information on a particular topic and may be broken down into several smaller modules. In a study, online learning modules were used by 86.4% of doctors who were in their 1st and 2nd years of professional work after graduating.[41] Newly qualified doctors valued e-learning as an adjunct to experiential and lecture-based teaching, and most preferred it as part of a combined learning program at work or at home.[42] A study has been done to evaluate the possibilities of internet-based radiation protection training among referring physicians.[43] From doctors answering the questionnaires, 75% found e-learning to be an easy way to study. Nineteen percent had previous experience in e-learning. Sixty-one percent found that it saved time, and 57% stated that they learned more effectively using e-learning in comparison to conventional lectures. In conclusion, doctors are very positive about internet-based learning.[43]

A weekly workload of 4.5 h may enable course participation even for busy clinicians.[44] E-learning brings with it new approaches to content development appropriate for postgraduate medical education. Emerging trends include an instructional design based on reusable learning objects and the semantic web. Those technologies will also facilitate online collaborative learning between trainees who are geographically and culturally different.[45]

The interactive potential of online CME and its flexibility in time and place offer potential improvements over traditional CME.[46] A trial was implemented to determine if internet-based CME can produce changes comparable to those produced through live interaction.[47] Physicians were randomly assigned to an internet-based CME intervention that could be completed in multiple sessions over 2 weeks, or to a single live, small-group, interactive CME workshop. Both interventions produced similar and significant immediate and 12-week knowledge gains, representing large increases in the percentage of items correct.[47]

Online versus Traditional Lecture-Based Learning

Several randomized controlled trials (RCTs) have been implemented to compare the online learning modalities versus offline learning modalities as detailed in Tables 1 and 2. E-learning may be equivalent to traditional learning regarding knowledge, skills, attitudes, and satisfaction. An RCT concluded that evidence-based online CME could produce objectively measured changes in behavior as well as sustained gains in knowledge that were comparable or superior to those realized from effective live activities.[47]

A randomized study assessed whether web-based learning was superior to face-to-face problem-based learning (PBL) in the setting of a 6-week cardio-respiratory course.[48] While virtual collaborative learning was as effective as traditional PBL regarding the acquisition of clinical reasoning skills, it was less well accepted than traditional PBL.[48] A study comparing online versus traditional classroom-based methods for teaching scientific writing was done. It was demonstrated that online scientific writing instruction was better than standard face-to-face instruction, in terms of writing quality and student

Table 1: Clinical trials comparing online versus standard offline learning methods

Authors	Trial	Modalities compared	Outcomes
Fordis *et al*.[47]	RCT	Internet-based CME versus live, small-group, interactive CME	Both interventions produced similar and significant immediate and 12-week knowledge gains
Raupach *et al*.[48]	RCT	Web-based learning versus face-to-face PBL in the setting of a 6-week cardio-respiratory course	Virtual collaborative learning was as effective as traditional PBL regarding the acquisition of clinical reasoning skills
Phadtare *et al*.[49]	RCT	Online versus traditional classroom-based methods for teaching scientific writing	The online group had better overall manuscript quality compared to the standard group
Subramanian *et al*.[50]	RCT	SS (a web-based) versus traditional lecture format in medical student learning and retention	The SS learning modality demonstrated a significant improvement in student learning retention compared to traditional
Yeung *et al*.[51]	RCT	CAL module versus the traditional text-/image-based learning supplements in the context of cranial nerve anatomy	No significant difference was identified between the CAL module and the traditional learning group

RCT: Randomized control trial, SS: StepStone Interactive Medical Software, CAL: Computer-assisted learning, CME: Continuing medical education, PBL: Problem-based learning

Table 2: Clinical trials comparing online versus standard offline learning methods

Authors	Type of trial	Modalities compared	Outcomes
Chenkin *et al*.[52]	RCT	Web-based tutorial versus didactic lecture for learning ultrasound-guided vascular access	There were no significant differences in mean objective structured clinical examination scores or written test scores between the web group and the didactic group
Platz *et al*.[53]	RCT	Computer lectures versus classroom lectures in basic ultrasound and the EFAS for trauma	Computer-based lectures are not inferior to classroom lectures in subjects without prior ultrasound education
Platz *et al*.[54]	RCT	Web-based didactics versus traditional method in basic ultrasonographic principles and the EFAS for trauma	Both the classroom and web group showed significant improvement in pre- and posttest 1 scores with similar knowledge retention after 8 weeks
Edrich *et al*.[55]	RCT	Web-based versus traditional classroom-based training of lung ultrasound for the exclusion of pneumothorax	Test results of groups, web and class, improved by a mean of 42.9% (±18.1% SD) and 39.2% (±19.2% SD) respectively, whereas the score of group control (no training) did not improve significantly
Maloney *et al*.[56]	RCT	Face-to-face traditional education versus web-based education for training health professionals in exercise prescription for falls prevention	Web-based and traditional approaches produced equivalent results in all of the outcome domains
Bello *et al*.[57]	RCT	Traditional versus online teaching for educating anesthesiology residents in the principles and practice of difficult airway management	Knowledge gains in the online group were slightly, but not significantly, greater compared with traditional group both in written (P=0.228) and practical skills (P=0.376) tests
Simonsen *et al*.[58]	RCT	E-learning versus classroom teaching for drug dose calculations for nurses	No differences in learning outcome or risk of error between e-learning and classroom teaching
Hearty *et al*.[59]	RCT	Textbook for case preparation versus textbook plus completed the e-learning module for case preparation by resident in the operating room	The e-learning group scored significantly better and demonstrated competence on the test compared with the groups using textbooks only

RCT: Randomized controlled trial, EFAS: Extended focused assessment with sonography, SD: Standard deviation

satisfaction.[49] Subramanian *et al*. concluded that the StepStone Interactive Medical Software (a web-based medical learning modality) modality demonstrated a significant improvement in student learning retention compared to the traditional didactic lecture format.[50] Yeung *et al*. failed to demonstrate a better contribution of the computer-assisted learning module to the understanding of spatial anatomic relationships of the cranial nerves in novice students.[51] In particular, no significant difference was identified between the computer-assisted module and the traditional text-/image-based learning supplements.[51]

The web-based tutorial was at least as effective as the traditional didactic lecture for teaching the knowledge and skills essential for learning ultrasound-guided vascular access. Participants expressed high satisfaction with this teaching technology.[52] Computer lectures in basic ultrasound and the extended focused assessment with sonography for trauma (EFAST) versus classroom lectures were compared.[53] Computer-based lectures were not inferior to classroom lectures and may represent a worthwhile substitution in subjects without prior ultrasound training.[53] Web-based ultrasonography and the EFAST didactics are comparable to traditional classroom lectures and result in similar knowledge retention in a study of two German emergency departments.[54] When training anesthesiologists to perform lung ultrasound for the

exclusion of pneumothorax, it was found that web-based training was not inferior to traditional classroom-based training.[55] A study of web-based and face-to-face approaches to the delivery of education to clinicians on the subject of exercise prescription for falls prevention produced equivalent results in all of the outcome domains.[56] An RCT was implemented to compare the effectiveness of traditional and online teaching methods for educating anesthesiology residents in the principles and practice of difficult airway management.[57] It concluded that online teaching formats may be a valid alternative for teaching residents the principles and practice of difficult airway management.[57]

In an RCT study, nurses from hospitals and primary healthcare were randomized to either e-learning or classroom teaching.[58] The learning outcome and risk of error were compared after a course in drug dose calculations with the two methods. The study showed no differences in learning outcomes or risk of error between e-learning and classroom teaching in drug dose calculations.[58] E-learning using the Computer-Enhanced Visual Learning platform significantly improved preparedness, confidence, and comfort with percutaneous closed reduction and pinning of a pediatric supracondylar humeral fracture by residents.[59]

Therefore, online methods are as effective as standard methods for training healthcare professionals in clinical interventions for the outcomes of knowledge and clinical behavior.

COVID-19 Disease and Its Effect on Medical Education

The COVID-19 outbreak rapidly transitioned into a worldwide pandemic. This development has had serious implications for public institutions and raises particular questions for medical schools. The effect of COVID-19 on medical education is therefore considerable. Several teaching hospitals in the UK have reported cases of COVID-19, with some hospitals suspending medical and observer students from attending.[11] The initial reaction in many countries was for healthcare facilities to reduce or even cease many clinical services, including the closure of clinics and postponement of medical appointments and elective surgeries. As a result of the pandemic, hospital activities (e.g., research and education) and virtual e-learning platforms are increasingly being explored to eliminate physical meetings.[60] As COVID-19 is identified worldwide, governments have imposed quarantines and travel restrictions on an unprecedented scale. The COVID-19 pandemic imposes restrictions on the mobilization of medical students, with classes being canceled and the teaching hospitals operating with "on-duty" shifts only, focusing on COVID-19 cases. This pandemic represents a unique challenge to education and healthcare services.[61]

Social distancing is the most effective preventing strategy until the development of a vaccine. This precludes medical students from gathering in auditoriums or group rooms. In response to COVID-19, medical education faculty have quickly transitioned the entire preclerkship curriculum to online formats that include content in the basic sciences, health systems sciences, and behavioral sciences. Small-group formats convene online in virtual team settings. Clinical skills sessions occur online or, in some cases, may be deferred. Examinations have also transitioned completely to relevant online settings.[62]

Conclusion

Online learning has the potential to make important contributions to medical education. Web-based training is an effective and efficient method for medical education. Distance online learning is expanding and replacing the traditional method. As the revolution of e-learning has begun, universities should develop e-learning materials to improve the learning experience, knowledge, and skills acquired by their students. In the era of COVID-19 crisis, it is important that the medical schools and academic centers worldwide learn from the experience and prioritize planning for virtual e-learning for medical students and residents.

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Case Report: Polycystic Horseshoe Kidney Incidentally Detected in a Male Geriatric Patient – Review of the Literature

Abstract

The case concerns a geriatric male patient who was hospitalized for gastrointestinal symptoms. Polycystic horseshoe kidney was incidentally detected during imaging. The spectrum of clinical manifestations is broad extending from asymptomatic patients (e.g., the presented case) to patients with acute deterioration demanding surgical treatment. Concomitant presence of renal polycystic disease and horseshoe anomaly is likely to bring closer the age of the presentation of renal failure, due to polycystic disease, and complicates the surgical technique for nephrectomy. Due to the rarity of the anomaly, there is lack of clinical experience, so is of clinical importance to report such cases.

Keywords: *Horseshoe kidney, polycystic kidney disease, renal failure*

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Introduction

Polycystic horseshoe kidney is a rare clinical condition. About twenty cases of polycystic horseshoe kidney have been reported in literature.[1,2] It is thought to represent two separate forms of renal disease, without genetic association involved. Horseshoe kidney is the most common renal fusion anomaly, occurring in about 0.25% of the population.[1] Polycystic kidney disease (autosomal-dominant polycystic kidney disease [ADPKD]) is a hereditary disorder due to mutations in the genes responsible for the expression of the proteins polycystin 1 (ADPKD1) and polycystin 2 (ADPKD2).[9] Horseshoe kidney occurs in 1/400–800 live births and ADPKD in 1 in 400–1000 live births.[2] It is usually asymptomatic but can be related with renovascular hypertension, renal stones, and ureteropelvic junction syndrome.[5] Concomitant polycystic disease is extremely rare, with an incidence of 1 in 134,000 to 1 in 8,000,000 live births.[2] The concomitant presence of renal polycystic disease and horseshoe anomaly is likely to bring closer the age of the presentation of renal failure, due to polycystic disease, and complicates the surgical technique for nephrectomy.[3] Ultrasound and magnetic resonance imaging (MRI) are the appropriate diagnostic tools.

Materials and Methods

The present case concerns of an 85-year-old male patient who reached the emergency department, with a history of vomiting for 4 days, without other concomitant symptoms. Physical examination revealed jaundice of the skin and white of the eyes, without edema. The initial clinical examination revealed blood pressure of 90/50 mmHg and pulse rate of 83 beats/min, with an average temperature. Cardiovascular and respiratory system examination had no remarkable findings. No signs of acute abdomen were detected, with a negative Murphy sign, while the right hypochondrium area was tender. The patient had a history of dementia, heart failure, coronary disease, and atrial fibrillation, receiving proper medication. The 2nd day, an increase of serum creatinine (2.2 mg/dl) and urea (137 mg/dl) levels were detected with concomitant acute renal failure. The initial abdominal ultrasound revealed the presence of polycystic kidneys, with imprecision of the lower poles, a sign indicative of horseshoe kidney. The MRI performed confirmed the condition showing a horseshoe kidney, with an isthmus of renal tissue linking the lower renal poles, and multiple renal cysts of varying sizes in the cortical as well as medullary regions [Figure 1]. No definite obstructive phenomena, lithiasis, or renal mass lesion was identified. No definite cysts were seen in the liver, pancreas, or seminal vesicles.

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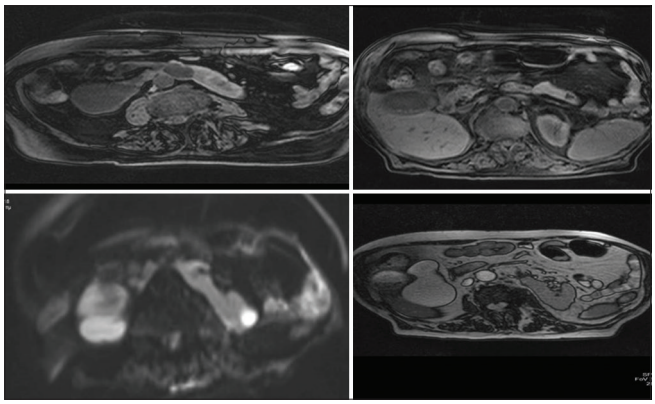

Figure 1: Magnetic resonance imaging: Multiple renal cysts of varying sizes in the cortical as well as medullary regions in a horseshoe kidney

Results

The diagnosis of polycystic horseshoe kidney was made, which was, in fact, an incidental detection, as the abdominal pain was due to concomitant cholelithiasis, with transient secondary deterioration of renal function. The patient was given conservative therapy with proper doses of antibiotics and hydration and maintained normal renal function until today. This patient presents an exception of this rare anomaly, which is likely to bring closer the age of renal failure presentation due to polycystic disease.[7]

Discussion/Conclusions

Polycystic horseshoe kidney is an infrequent clinical condition, which consists of a combination of two separate renal anomalies: one hereditary and one fusion anomaly. ADPKD is a hereditary disorder due to gene mutations and the third most common cause of end-stage renal disease.[3] Horseshoe kidney is the most common of all renal fusion anomalies and is often asymptomatic.[8,4] Polycystic horseshoe kidney is, however, extremely rare, with only twenty cases reported in literature,[1] with incidence ranging from 1 in 134,000 to 1 in 8 million cases.[10] Early recognition is of great importance for prevention of renal failure due to polycystic disease. The appropriate diagnostic tools are ultrasound and MRI.[10] Coexistence of renal polycystic disease and horseshoe anomaly is likely to shorten the age of renal deterioration and failure and therefore demands closer surveillance of these patients, despite the incidental diagnosis.[3] Patients with adult polycystic kidney disease usually develop renal failure after 40 years of age.[3] The clinical presentation includes abdominal pain, headache, and hematuria. Treatment for such patients consists of individually handling hypertension and serious complications including pain, hematuria, infection, nephrolithiasis, diverticulosis, and arterial aneurysms.[9] Isthmus undivided bilateral nephrectomy has been reported in polycystic horseshoe kidney patients.[6] This case, probably consisting an exception to the rule, tells us to keep in mind that the age of renal failure for these patients differs from individual to individual, so close surveillance of renal function is needed. Formulation of guidelines for management of these cases should be based on the clinical manifestations of the disease, and this is the reason to report this case.

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Conflicts of interest

There are no conflicts of interest.

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Traumatic Testicular Dislocation – A Case Report

Abstract

We report a motorcyclist who presented with a case of empty scrotum and bilateral dislocated testes in the groin after a blunt scrotal injury. Ultrasound and computed tomography revealed viable testes. Manual reduction was performed with success under anesthesia following orchidopexy. The patient made an uneventful recovery.

Keywords: *Blunt trauma, case report, dislocation, empty scrotum, testicles, urology*

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Introduction

Traumatic testicular dislocation is a rare clinical sequel complication of a blunt trauma of the scrotum or abdominopelvic injury and may be overlooked because of associated major injuries.[1] Its diagnosis depends on the awareness of the physician of its possible occurrence.[2]

It takes place after direct pressure on the scrotum rupturing the fascia of the spermatic cord[3] and dislocating one or both normally located testes out of their normal position[4] to the surrounding tissue, usually the inguinal region. Traumatic dislocation of the testis (TDT) occurs more often at the time of injury, but it has been recognized as a later event in a few cases.

The condition mainly occurs in younger men with a mean age of 25 years.[3]

Although diagnosis can be made by physical examination or with the use of examinations such as Doppler ultrasound (US) and computed tomography (CT), it is common for cases to go undetected and undiagnosed.

Motorcycle collisions are the most frequent mechanism cause today. Dislocation usually results from straddle injuries.[4] Cremasteric muscle spasm is a major contributing factor. It is important to prevent any delay in diagnosis as this can lead to loss of spermatogenic function of the testis, malignant transformation, and increased risk of orchiectomy.

Manual reduction of the dislocated testis is a quick, convenient treatment option for preservation, but it has a very high rate of failure because of the "buttonhole" defect in the coverings of the cord and the accompanying edema[5] and may overlook coexisting injuries.[6,7]

Case Report

A 47-year-old motorcyclist presented at the emergency department of our hospital after a road traffic accident, with multiple injuries and fractures (right ankle, left wrist, left femur, right shin, and left knee) and an empty scrotum upon physical examination.

He reported that during the accident, his motorcycle collided with a car and was knocked against the handlebar.

At presentation, he was fully conscious, oriented, hemodynamically stable, and neurologically intact.

On physical examination, tender soft masses were palpable in the groin. The perineum and penoscrotal region had minor abrasions, and the empty scrotum had no swelling or ecchymosis after sustaining the straddle injury [Figure 1].

He had no medical or surgical history and no genitourinary problems at the moment. He denied cryptorchidism, undescended/retractile testis, or inguinal hernia.

US and CT scan confirmed that the testicles were of normal size and had adequate blood supply. The left testicle was located in the inguinal canal and the right testicle at the external inguinal ring [Figures 2-4].

Both testicles were of normal size. The right testicle had heterogeneity upon US

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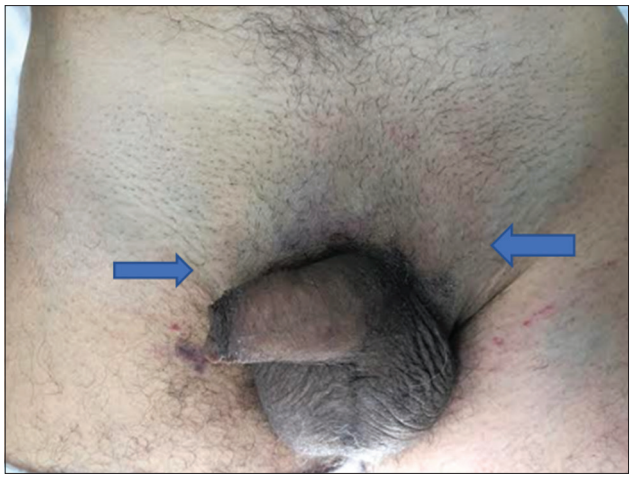

Figure 1: Palpable masses in the groin, indicating the position of the dislocated testes

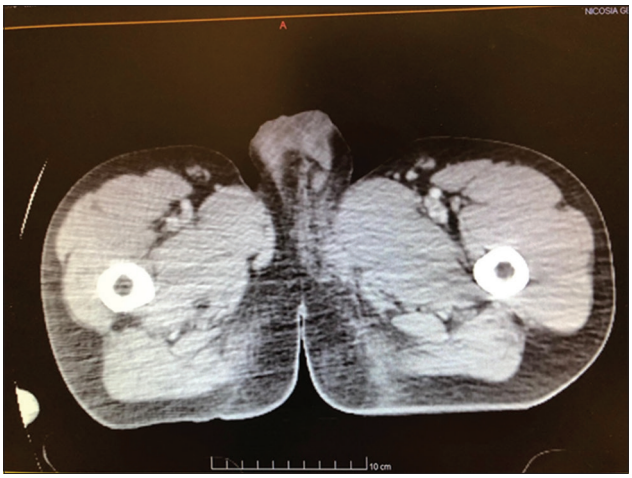

Figure 2: Computed tomography scan confirming an empty scrotum

Figure 3: Axial computed tomography scan presenting the left testicle in the inguinal canal

Figure 4: Axial computed tomography image presenting the right testicle at the external inguinal ring

revealing intraparenchymal contusions. The left testicle had an area of low attenuation being 1,7 cm in diameter, indicative of an intraparenchymal hematoma. The tunica albuginea and vaginalis seemed to be intact bilaterally.

Overall, CT brain was normal, CT of the cervical spine and chest with no pathological findings. CT abdomen showed additional fractures to the ones mentioned above including a cross-sectional fracture of the right O1 vertebra and stable fractures upon the pelvic bones.

The patient was taken to theater for immediate assessment by the urology and orthopedic surgeons, with good vital signs and in a stable condition.

After anesthesia, a closed manual reduction of the testes to the scrotum bilaterally was performed easily. Both testicles were palpated and revealed no signs of edema or excessive injury. It was considered profitable for the patient to undergo exploratory scrotal surgery and orchidopexy. Surgery confirmed apparently healthy and viable testes, with normal spermatic chords, and so they were fixated to the dartos muscle.

As far as the genitals are concerned, the patient recovered well.

Follow-up physical examination and US at the 7th, 30th, and 60th postoperative days at the outpatient clinic were normal. The preoperative findings on US had adequately subsided, and the patient was asymptomatic. The wound healed well.

Discussion

Blunt scrotal trauma is a common injury in young men and is usually caused by getting kicked or hit by a ball and motorcycle and bicycle accidents.[8]

It can be a cause of several testicular injuries such as minor contusions, hematoma, ruptured tunica, and even completely shattered testicles.[7] It causes about 85% of testicular injuries.

Traumatic testicular dislocation, also referred to as traumatic luxation of the testis, is an uncommon consequence of blunt testicular trauma.

It was first described by Claubry in 1809 when a victim had been run over by a wagon wheel.[1,6]

It is difficult to determine the actual incidence because it is likely to be underreported.[1,7] Bilateral dislocation is even less common (30% of patients) and constitutes about one-third of all cases. A recent review concluded that less than 200 cases had been notified in literature around the world.[1,4]

Most cases result from straddle injuries during high-speed motorcycle collision accidents when the rider is propelled forward with traumatic impact of the perineum and scrotum over the fuel tank or handlebar. The shape of fuel tank wedges the groin area, forcibly displacing the testis into superolateral direction.[4] The testicle passes through the smooth loose coverings of the cord until it bursts through them, after rupture of the fasciae (external, cremasteric, and internal), and comes to lie in the superficial inguinal pouch anterior to the external oblique aponeurosis, at the level of the external ring.[1,9] In its superficial location, the testicle is covered only by skin, subcutaneous tissue, and deep fascia.[10]

Nonetheless, possible locations of a dislocated testis include the superficial inguinal (50%), pubic (18%), canalicular (8%), penile (8%), intra-abdominal (6%), perineal (4%), and crural (2%) regions. Rarely, in association with pubic bone fracture, retrovesical dislocation can be found.[1,7] Goulding has classified traumatic testicular dislocation in three categories as seen on Table 1.[11,12]

Although TDT occurs more often at the time of injury, in a few cases, TDT has been recognized as a later event.[1]

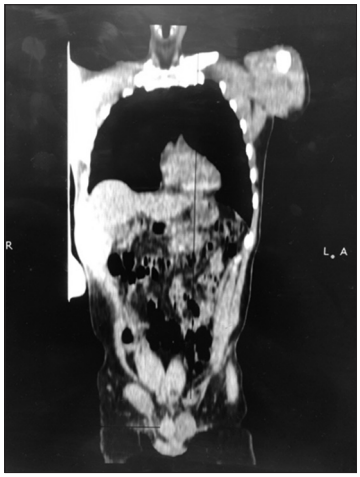

Figure 5: Coronal computed tomography image presenting both dislocated testicles

There is not a specific method to differentiate between truly undescended, retractile testes, traumatic testicular torsion, high-lying testes,[4] and those that sustained traumatic dislocation. The clinical history and physical examination have a crucial part in the investigation.[4]

The ultimate location of testicular dislocation is related to the mechanism of injury, the direction and intensity of the impact, the presence of anatomic abnormalities, and a brisk contraction of the cremaster muscle at the moment of trauma, associated with a secondary cremaster muscle spasm contraction.[4]

The most common factor contributing to the dislocation of the testis is cremasteric muscle reflex, which can forcefully retract the testis out of the scrotal sac, wide external inguinal ring, indirect inguinal hernia, and atrophic testis.[1,6,7]

A thorough physical examination defines the diagnoses of an empty scrotum with possible palpable masses. Doppler US is traditionally the primary investigation used to evaluate the viability and blood flow to the testis[7] and diagnose hematoceles and hematomas, testicular rupture, ruptured tunica, torsion, epididymal avulsion, minor contusions, and completely shuttered testes.

Moreover, the presence of this type of injury can be very useful in the course of medicolegal investigations of a fatal motorcycle accident, helping to identify the motorcycle driver and to determine responsibilities in the accident.[4]

In difficult cases, CT may be needed to locate the gonads [Figure 5].

Manual reduction is the initial treatment of choice for a normal testicle without coexisting injuries. Manual reduction is the initial treatment of choice for a normal testicle without coexisting injuries. However, it is successful in only 15% of patients. This can be attempted at the emergency department when detection is early and the testicle is palpable. Manual reduction may also be attempted in the first 3–4 days after dislocation when the edema has subsided and before adhesion formation.[1,10]

Delayed reduction of a dislocated testicle in postpubertal men has been reported to impair spermatogenesis, which is usually detected 4 months after the dislocation takes place. The histological changes in these patients are hyalinization and atrophy of seminiferous tubules, absence of sperm or spermatid formation, presence of germ cells, and an

Table 1: Goulding's TDT classification

Testicle location	Description
Internal dislocation	Testis displaced through the external inguinal ring into the inguinal canal or abdominal cavity
Superficial dislocation	Subcutaneously dislocated testis in an area with the external inguinal ring as the center and length of spermatic cord from it as the radius
Complex/compound dislocation	External displacement of testes through lacerated scrotum

TDT: Traumatic testicular dislocation

increase in alternative germ cells. However, various reports have shown that once the condition is treated, the prognosis for recovery of the endocrine function and fertility can be excellent.[7,12]

Further potential complications of delayed reduction include torsion, testicular ischemia, acute and chronic discomfort interfering with daily activities, and malignant transformation.[1,4,6]

Surgical exploration and orchidopexy should be performed early to evacuate hematoma, repair lacerated tissue, and fix the testicle after repositioning it.[4]

Goulding suggested that for traumatically dislocated testes located in the abdomen that are not relocated (e.g., with prolonged delay of diagnosis), the testicle should be surgically removed because of the theoretical increased potential for a neoplasm to develop. The hypothesis of a postdislocation neoplasm is unproven.[12]

Conclusions

Testicular dislocation is a rare sequel of blunt scrotal injury, which carries with it many risks and is easily overlooked.[13,14]

The empty scrotal sac leads the investigation!

With proper management, prognosis is excellent.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

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