

Current Researches in Surgery Medical Sciences

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# Surgery **Medical** Sciences

**Editors**

Prof. MD. Ph.D. Goran KRSTACIC  
MD Ahmet YILMAZ



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Prof. MD. Ph.D. Goran KRSTAČIĆ

MD. Ahmet YILMAZ



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# Preface

*Current Research in Surgery Medical Sciences* is serving an academic forum for both academics and researchers working in such fields. Surgery medical sciences research is an interdisciplinary by nature. So it covers several fields Besides, have been used as a research method for the contemporary issues relevant to surgery medical sciences. In this book, the academics working in different fields share their results with the scientific community. Thus more researchers will be aware of these studies and have some new ideas for their future studies. The selected articles have been reviewed and approved for publication by referees. It is hoped that the book will be of interest and of value to academics and researchers

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# Referee Board

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# Chapter I



# Determine the Length of the Fibula in Ankle Fracture: A Radiologic Study

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## **Introduction**

Ankle sprains and fractures are among the most common musculoskeletal injuries (1,2). Fractures with less than 3 mm lateral malleolar displacement without talar displacement are considered stable and treated conservatively, while external fractures are considered unstable and are treated surgically.

In surgical treatment of ankle fractures, good results are achieved with anatomic restoration, a lengthened fibula and a functional syndesmosis (3). The most important structure of ankle fractures starts from the lateral structures and lateral structures account for about 60-70% of the stability. Other factors in stability are medial ligament osseous complex and syndesmosis, respectively (4).

In ankle fracture surgery, fibula length is the primary condition for foot biomechanics and ankle mortise. A possible shortening of the fibula accepted as a factor in the displacement of the tibiotalar contact. Even 1 mm displacement in tibiotalar reduces tibiotalar contact by 40% (5). Curtis et al. reported that 2mm fibular shortening resulted in a 30% external rotation of the ankle associated with decreased joint contact(6). Evaluation of the lateral malleolar length can be performed radiologically with the presence of talocrural angle and shenton line on direct radiography (7,8). Radiological measurements such as tibiofibular overlap in syndesmosis injury, tibiofibular clear space and medial clear space measurements can be used in the diagnosis of syndesmosis injury (9). There are no radiological measurements in the literature to evaluate lateral malleolar length. Radiological measurements are necessary for the evaluation of length of lateral malleolus, which is one of the most important surgical targets for both stability and ankle mortise. In our study, both the markers used for

fibula length were evaluated and radiological measurements were investigated to determine the length of lateral malleolus.

### **Material and methods**

Between January 2018 and March 2018, patients who presented to our outpatient clinic with foot complaints and without trauma were examined. The radiographs were retrospectively gathered through the Picture Archiving and Communication System (PACS) system at our institution. We obtained ethics approval through the Health Research Ethics Authority. Patients with a range of 22-75 years of age and with standard direct radiographs were included in the study. Patients with non-standard radiographs, patients with congenital deformity and past surgical history were excluded from the study. Three orthopaedic surgeons (U.Y., M.U., and Y.P.) reviewed 150 ankle radiographs. Age, gender of the patients were recorded. Presence of the circle sign and Shenton's line on AP graphs and mortise graphs were evaluated and additionally radiologic measurements of the distances of tibial plafond-distal fibula, distal medial malleolus-distal fibula, talus distal lateral process-distal fibula and talocrural angle were performed by using radiographs with or without bearing load.

### **Radiologic Measurements**

Evaluation of fibular lengths of patients; AP and mobile bearing load AP view de talocrural angle (Figure 1), AP and mortise view with Shenton's line and circle sign presence (Figure1) and radiological measurements of AP and mobile bearing load AP view also tibial plafond-fibula distal, medial malleolus distal- The distal of the fibula was measured by distance measurement of the distal lateral process of the distal fibula (Figure 2).

### **Statistical Analysis**

Data was analysed by using SPSS 22 Windows Package Programme and 95% confidence interval (CI) was performed. Priorly, frequency distribution was used for qualitative variables while minimum, maximum and median values were used for quantitative variables in our statistical analysis. Median values and deviations were calculated in the measurements (distal tibia plafond-fibula distal, medial malleol distal-fibula distal, distal to fibula-talus lateral process), and the relationship between the values according to age and sex was examined by Mann-Whitney U test. Chi-square test was used to evaluate the presence of Shenton line and circle sign according to AP and mortise view.

## Results

The mean age of the patients was 42.7 (23-72), there were 60 male and 40 female patients. The male/female ratio was 1.5/1. Bilateral ankle fractures were noted in fifty patients and remaining patients have unilateral ankle fracture (26 right and 24 left). Talocrural angle was measured as  $8 \pm 1.4$  (6-12) degrees on AP radiographs and  $7.6 \pm 1.6$  (4-11) degrees on mobile bearing AP radiographs ( $p = 0.892$ ). The evaluation of fibula length with Shenton's line was found to be 10% on AP radiographs, and 82% on mortise graph ( $p = 0.000$ ). Shenton's line finding as an indicator of shortening of the fibula was positive on only 10% of AP radiograph, while positive on 82% of mortise graphs. ( $p=0.000$ ). The evaluation of fibula length with circle sign was 18% on AP radiographs, and 86% on the mortise graphs ( $p = 0.000$ ). Of the radiologic measurements, the narrowest tibia plafond-fibula tip was measured as  $29 \pm 2, 4$  (26-33) mm. One of the other measurements was the distances between the medial malleolus distal-fibula distal were measured as  $13 \pm 4.1$  (7-20) mm.

The tibial plafond-fibula tip was measured as  $28,6 \pm 2,3$  (24-33) mm and similarly the medial malleolus distal-fibula distal was measured as  $12.6 \pm 3.6$  (7-18) mm, on graphs with loaded ( $p=0.560$  and  $p=0.645$  respectively). The distal fibula tip-talus lateral progress measurements were  $6 \pm 1.8$  (5-10), unlikely the distal fibula tip-talus lateral progress measurements decreased in the radiographs ( $p = 0.020$ ) (**Table 1**).

Fibular tip measurements with tibial plafond were measured as  $28.7 \pm 2.1$  (26-33) mm below 40 years of age and  $29.5 \pm 2.4$  (26-33) mm above 40 years of age. According to gender, tibial plafond and fibula tip were  $27.6 \pm 2$  mm in females and  $30.8 \pm 2.3$  in males, respectively. Bilateral patients showed parallelism between tibial plafond and fibula tip. **Table 2** shows the differences between radiographic measurements and demographic changes.

## Discussion

Lateral malleolar fixation in ankle fractures is principal requirement for ankle stability. Apart from stability, fibula fracture reduction and fixation of the talus primarily provide reduction (10). While the easiest way to achieve the anatomical restoration of fibula is open surgical approach, anatomic reduction may be difficult in segmental and segmental fractures. Appropriate length and rotation were obtained with the bridging plate method or intramedullary fixation in segmented fractures. Apart from segmented fibula fractures. In coexistence of AO43 with fibula fractures, it is difficult to achieve a fibula length with open reduction and markers to evaluate

the length are required. Although there is no priority fixation method for long oblique or spiral fractures, intramedullary fixation is recommended especially in transverse fibula fractures and elderly patients (to reduce the risk of complications) (11,12). For intramedullary fixation of the fibula, length and rotation alignment is also targeted in surgery.

Three methods commonly used to evaluate fibula length consist of the measurement of the talocrural angle (7), evaluation of the tibiofibular (Shenton) line (8), and detection of the dime sign (circle) (9). Due to the difficulty in obtaining these images at all times. We consider that additional radiological measurements (as mm) likely to be helpful for surgeons in intraoperative or postoperative evaluations.

In order to evaluate the fibular length, in order to obtain radiologic measurements used for detection of syndesmosis injury such as tibiofibular overlap, tibiofibular clear space and medial clear, tibial plafond-distal fibula tip, medial malleolar tip-distal fibula tip and distal fibula tip-talus lateral process were measured. Measurements were evaluated in terms of variation and mean values. In our study, the most reliable results for AP view (less deviation of standard deviation and easy radiological detection) were observed between tibial plafond and fibula tip. The mean value of the tip of the fibula with the tibia plafond was  $29 \pm 2.4$  (26-33) mm. There was a shortening between tibial plafond and fibula tip in female gender,  $27.6 \pm 2$  in females and  $30.5 \pm 2.3$  in males. There was no difference according to age.

Fibula malunion causes are often fibula shortening and external rotation problem (13). This is why fibula length assessment is frequently encountered in malunion studies in the literature (14, 15). Three markers including the lines of the tibial plafond and surface of the talar dome should be parallel, tibiofibular Shenton's line and circle sign are used to evaluate the fibular length (16). While tibiofibular Shenton's line and circle sign have been described in some studies in mortise radiographs, some studies have not provided information about correct radiography. Both AP and mortise radiographs were imagined and tibiofibular Shenton's line with circle sign were evaluated. While the detection of Shenton line circle sign on AP images was 10-20%, this rate increased to 80-90% on mortise radiographs.

Talocrural angle is also helpful to evaluate the length of the fibula. Presence of this angle between  $<75-86$  degree interval and decreasing more than 3 degree of this angle on the opposite side indicates fibular shortening. It has been found that one degree decreasing in talocrural

angle was related with fibular shortening as 1 mm (17). While talocrural angle can simply be measured with PACS system, it is difficult to evaluate it intraoperatively. Talocrural angle was measured as  $8 \pm 1$ , 4 (6-12) degree in our study while consistency was high. However we also think that it is difficult to use intraoperatively. The distance between the tibia plafond and the tip of the fibula were observed as  $29 \pm 2.4$  (26-33) mm and this value was the narrowest range of radiologic measurements in our study. Medial malleolus type was easily observed from the other scales and the difference between the measurements was observed as  $13 \pm 4$  (7-20) mm. While the distance between distal fibular tip and talus lateral process was measured as  $8 \pm 2$  (7-12) mm, doctors have no consensus on the measurements of talus lateral process. Measurements in graphs bearing load were parallel in terms of tibial plafond- fibular tip, the distal of medial malleolus-distal were parallel whereas there was a decrease in distance from the distal of the fibula to the lateral processus.

In the literature, Panchbhavi et al hypothesized that there was a variance between the fibula tip and the lateral talar process, such as between Radius and ulna on the wrist, and found a significant relationship between the tip of the fibula tip and the talus tip. They found a significant correlation between distal fibula and talar process in graphs with loaded and also facilitated the visualization of lateral processus on the radiologic examinations.

In trauma patients, there is a lack of load-bearing standard radiographs. In our study, the relationship between distal tibial plafond, medial malleolar tip, lateral talar processus tip and distal fibular tip was examined on both radiographs and without load. (18) Scales previously determined for syndesmosis injury were interrogated and were compared with the demographic data such as age and gender in terms of changing (19). In our study, tibial plafond and fibula tip measurements were evaluated according to age, sex and sides in AP view. There was no significant difference in terms of age and side. Female mean values were 2.5 mm lower than men. Also, bilateral measurements were 1mm lower on the left side than the right side. The strengths of the study were the adequate number of patient radiographs, the presence of sufficient bilateral radiographs, the appropriate radiographs of PACS by experienced technicians, and approval by three orthopedic and traumatology physicians. The measurement of the patients with radiographs without burden and burden strengthens the study in the evaluation. In our study, although both Shenton's and circle sign were not seen on each mortise radiograph, it may be due to variation in angle of patient-based

mortise radiograph. The number of patients remained limited for changing of data according to demographic data such as age and gender for this study. Additionally being regional of our study is an obstacle to the universalization of values.

### **Conclusion**

The presence of circle sign in 85% and Shenton's line in 82% in mortise graphs showed the reliability of these graphs. The most reliable results in AP views are related with the measurements of tibial plafond-fibular tip and measured as  $29\pm 2,4(26-33)$  mm. The distance between the tibial plafond and distal fibula was measured as  $28,5\pm 2$  mm in females and  $30.5\pm 2$ mm in males. Shortening was observed in female sex, whereas there was no significant difference in terms of age

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**Table 1:** Radiografic measurement

	AP view	Mortis view	Mobile bearing AP	p
Circle sign				
Yes	27 (%18)	129 (%86)		0.000
No	123 (%82)	21 (%15)		0.000
Shenton line				
Yes	30 (%20)	123 (%82)		0.000
No	120 (%80)	27 (%18)		0.000
Talocrural angle				
Mean	8		7,6	0.892
Std	1,4		1,6	
Minimum	6		4	
Maximum	12		11	
Tibia plafond fibula distali-distal				
Mean	29		28,6	0.560
Std	2,4		2,3	
Minimum	26		24	
Maximum	33		33	
Medial malleol distali-distal fibula				
Mean	13		12.4	0.645
Std	4		3,6	
Minimum	7		7	
Maximum	20		18	
Distal fibula ucu- talus lateral proces				
Mean	8		6	0.020
Std	2		1,8	
Minimum	7		5	
Maximum	12		10	

**Table 2:** Radiologic measurement of demographic variable

	Tibia plafond- fibula distali	Std	p	Medial malleol distali - fibula distali	Std	Fibula distali- talus incisura	Std
Age							
<40	28.7	2.1	0.340	10.8	3.9	7.8	1.9
>40	29.5	2.4		11.2	3.9	8.1	1.8
Gender							
Male	30.8	2.3	0,081	12.1	3.3	8.4	1.8
Female	27.6	2		10.4	3.1	7	1.5
Bilateral							
Left	28.6	2.4	0.230	10.5	3.7	7.2	1.7
Right	30.3	2.4		11.7	3.6	8.3	2

**Figure 1**

Talocrural angle (a) AP view and mobile bearing AP view, None Shenton line , circle sign in AP view and Shenton line (b) , circle sign (c) in mortis view



**Figure 2**

Radiologic measurement AP view and mobile bearing AP view



Tibia plafond-fibula distali(T.P.-F.D.), medial malleol distali-fibula distali (M.M.-F.D.), fibula distali- talus lateral proces distali (F.D.-T.L.P.D.)

## **Chapter II**

# Can we Predict the Accurate Acetabular Cup Size with Digital Templating in Complex Total Hip Arthroplasty?

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## INTRODUCTION

Templating is one of the crucial steps of the preoperative planning for a successful total hip arthroplasty (THA) surgery. Prior determination of the appropriate implant size get in favour in terms of avoiding company based problems, decreasing the operation time as well as the complication rates. As the digital radiography methods and software programs are developed, the templating methods gained a different dimension. However, manual templating with conventional radiographs is the onset of templating <sup>1,2</sup>. Digital templating, a new technology, is being routinely practiced in clinical settings with the advantage of being fast, precise, and cost-effective. There are so many reports about digital templating methods in the literature revealing a decreased accuracy of acetabular component when compared with the femoral component, regardless of the different surgery types in these previous studies <sup>3,4,5</sup>.

Acetabular component fixation is the most struggling step of the THA operations. Thus, increased inconsistency of preoperative assessments especially in complex cases should be an issue to be investigated.

The primary reason of the low accuracy rates is the variability of reference points in complex cases. Particularly in developmental dysplasia of hip (DDH) cases; the factors leading to variations of crucial reference points and negatively affecting the measurements are thought to be the osteoporosis of the actual acetabular walls, excessive

retroversion, abnormal structure and the misplacement of the femoral head resulting with the false acetabular development, implanted materials to the proximal femur, prior surgeries, and soft tissue pathologies <sup>6,7</sup>.

During the surgery, the acetabulum is rimmed in 2 mm increments till a good fit is obtained. The rimming is done till the subchondral bone is just exposed. The uncemented cup either of the same diameter or one-two millimetres bigger is than jammed as a press fit into the rim acetabulum. If the fit is not exact, the cup would either be too loose or may not be seated adequately in the acetabulum. This may lead to dislocations, or acetabular wall fractures. These complications are more common in complex hip joint operations, in particular. Thus preoperative preparation stage gains more importance.

On these aspects, we aimed to evaluate the accuracy of preoperative digital templating in particularly determining the acetabular component size of complex hip joints.

## **MATERIAL AND METHODS**

This study was carried out with the approval of the local ethics committee of clinical research of Duzce University with the decision numbered 119/2018. We evaluated the primary THA surgeries between 2017-2019 in our hospital and only complex cases with deformed femora-acetabular congruence and anatomic structures (Avascular necrosis (AVN), DDH, previous surgery, arthrodesis) were enrolled in the study. To determine the accuracy and reliability of digital templating, 40 cases of primary THA with complex hips were retrospectively reviewed.

### **Preoperative Planning and Templating**

Preoperative digital template was performed using the Sectra ID-7 (Uniview PACS Teknikringen 20 SE-583 30 Linköping Sweden ). Standard radiograph of the hip were taken including an antero-posterior (AP) and cross table lateral view. The AP pelvis x-ray was made with the patient supine and both legs internally rotated 15 degrees and the x-ray beam centred on the pubic symphysis. The preoperative templating was done by the same surgeon who performed the THA.

Accuracy of preoperative planning was determined as described before by comparing the difference between planned and implanted component sizes as documented in the surgical report <sup>8,9</sup>. Perfect matches and a variance of +/- one size were considered to be adequate. Deviations of more than one size were considered inaccurate.

Calibration was made by the set magnification manually on digital screen. some studies have shown the use of a set magnification to be more accurate than calibration with an external calibration marker <sup>10,11</sup>.

### **Operative Procedure**

Surgery was performed using a similar posterior approach, surgical and uncementing technique <sup>12</sup>, and enhanced posterior soft tissue repair <sup>13</sup>. All operations were performed using a posterior approach by same surgeons and in every case, a cementless Trilogy cup (Zimmer, Warsaw, Ind.) was implanted with a 2-mm press fit technique <sup>14</sup>. 5 five hips required auto transplantation of bone from the femoral head to optimize coverage of the acetabular cup. The 9 hips were considered being completely covered. Four hips underwent femoral osteotomy.

The digital plan was used during surgery. The distance between the lesser trochanter and K-wire which fixed 2cm proximally from superolateral border of the acetabulum used to determine limb length prior to dislocation. The altitude of the neck cut, as determined in the preoperative plan, was reproduced with a ruler. Exposure of the acetabulum included routine identification of the anterior and posterior margin of the acetabulum and the cotiloid notch. The hemispherical reaming of the acetabulum was started by medial reaming up to the lateral wall of the teardrop, followed by reaming in the cephalad direction of the natural acetabular opening, to reproduce the medialisation and lateral coverage of the cup as predicted in the digital plan.

### **Statistical Analysis**

Intra-observer variability for observer was analysed using intra-class coefficient (ICC) for acetabular cup size and Cohen's kappa (k) for offset and stem size. All statistical analyses were undertaken using Statistical Package for Social Sciences (SPSS) v.22 software package (SPSS/PC Inc., Chicago, IL.). Differences were compared using the chi-square test for nominal variables or summarized data with or without continuity correction when appropriate. The t-test was used for a comparison of continuous variables at an alpha error of 0.05.

### **RESULTS**

With respect to inclusion criteria, 40 cases were included in this study. %62.5 (n=25) were female and %37,5 (n=15) were male patients. The mean age was 49,8 ( $\pm$  12.1) years. Left hip pathology was detected in 26 (65%) patient whereas right hip was in 14 (35%) patients. There were 11 cases type I, 6 cases of type II and 8 cases of

type III dysplasia hips according to Crowe classification<sup>15</sup>, 9 AVN, 4 previous surgery and 2 cases arthrodesis. (Figure-1)

### General Reliability

The exact cup size was predicted in 17,5% (n = 7). Further, 22,5% (n = 9) were within a range of +/- one size. Thus, 40 % (n = 16) of the cups have been measured accurately. Two sizes smaller in three cases and tree sizes smaller in three cases. In 18 patients (45%) predicted sizes were more than 3 sizes. Data of cup planning accuracy are presented in Table -1.

32,5% (n = 13) of the stems were predicted correctly, whereas further 42,5% (n = 17) were within +/- one size. Altogether, stems were estimated correctly in 75% (n = 30). Data of stem planning accuracy are presented in Table -1.

Especially in patients with DDH accuracy of digital templating rates was low. In our aspects the damage on the acetabular walls was the cause of it. Table-2

### Sex and Planning Accuracy

Femoral components have been planned correctly in 64% (n = 16 ) for female patients and in 73,4 % (n = 11 ) for male patients. Cup planning has been adequate in 36 % (n = 9) for females and in 46,6 % (n = 7) for males. Analysing gender differences, Mann–Whitney U test showed no statistical significant difference, too (stem: p = 0.13; cup: p = 0.061).

**TABLE-1: Planning accuracy and deviation of implants in absolute values and percentage**

Implant size	Stem	Occurance	Acetabular Cup	Occurance
Perfect match	13	32,5	7	17,5
+/- 1 size	17	42,5	9	22,5
+/- 2 size	6	15	3	7,5
+/- 3 sizes and more	4	10	21	52,5

**TABLE-2: Accuracy of different cases**

<b>Accuracy of cup size</b>	<b>DDH</b>	<b>AVN</b>	<b>Arthrodesis</b>	<b>Previous Surgery</b>
<b>Perfect Match</b>	3	4	-	-
<b>+/- 1 size</b>	2	5	-	2
<b>+/- 2 size</b>	3	-	-	-
<b>+/- 3 sizes and more</b>	17	-	2	2

## **DISCUSSION**

In the last decade, favourable results have been reported from THA operations due to the developing technology, and surgical procedures. Preoperative planning is crucial in complex hip joint operations. The utility of digital radiology and software programs, in particular, prevents most of the surgical complications that may emerge.

Benefits of preoperative templating include estimation of true acetabular and femoral component sizing, appropriate restoration of preoperative offset, correction of leg length discrepancy (LLD), and anticipation of special componentry or techniques<sup>16</sup>. Templating also helps the surgeon minimize guesswork and plan for potential intra-operative problems.

However, it is uncertain whether digital templating is suitable for complex THA resulting from severe deformity, such as DDH, AVN, arthrodesis, and previous surgery. To the best of our knowledge, few reports have studied the accuracy of digital templating in THA with regard to dysplastic hips<sup>3,4,5</sup>.

Unnanuntana et al. found that when acetate templating was used, predictability of the cup size was much poorer than that for the femoral component. According to the authors, one of the factors explaining this reduced accuracy was that 62.4% of the patients in the series had dysplastic hips<sup>17</sup>. In our study accuracy was 26,3 % in the patients with DDH . These lower accuracy rates are thought to results from the variance of reference points necessary for measurements in software programs.

Factors affecting the results of measurements are summarized as experience, and calibration problems, manual templating, increase of

the body mass index (BMI), DDH, previous surgeries, existing implants and soft tissue pathologies in the literature <sup>17,18</sup>.

Xin Zhao et al. revealed out that the predictability of THA in patients with dysplastic hips was 48.8% for cup size and 73.2% for stem size. It was mentioned that one of the factors of reduced accuracy is combining medialisation or proximalisation of the acetabular cup with various techniques for stable implantation <sup>19</sup>.

Assessment of actual acetabulum inferior border is very important in acetabular component replacement. Especially in dysplastic hip, determining the transvers acetabular ligament which is one of the reference points, may be challenging due to the hypertrophic soft tissue, and excessive osteophytes in that area<sup>19</sup>. (Figure-2)

Despite attempting to place all components in the true acetabulum, the acetabula analysed by Stans et al. [18] were placed outside the true acetabular region in 25.7% of Crowe type III dysplastic hips compared with 12% in Crowe type II <sup>20</sup>. The predictability of the cup size was more affected than that of the stem size in the preoperative templating of dysplastic hips.

In a subluxating, displastic hip lower load transmitted to the anatomical acetabulum leading to a loss of bone stock <sup>21</sup>, that can be compromise the cup fixation and malposition of cup so to concern the accurate size whining  $\pm 1$  size in digital templating is more realistic<sup>22</sup>. (Figure-3)

It was mentioned by Gamble et al. that digital templating had an accurate prediction for the acetabulum in 38% of the cases and traditional onlay technique on hardcopy radiographs printed from digital radiography had an accuracy of 20% for the acetabulum. However, when the cases within 1 size of the actual implant are included, the accuracy improved dramatically to 80% for the acetabulum by digital templating and 60% by using onlay templating <sup>22</sup>.

More recent studies have shown similar accuracy for sizing implants to within 1 size for both digital (cup 60%-81% range, stem 74%-94% range) and analogue (cup 67%-97% range, stem 77%- 98% range) templating <sup>3,17,23,24</sup>.

It is essential to perform proximal femoral osteotomy in most of the Crowe Type 3-4 DDH cases but stiffness of the soft tissue may cause high vertical offset and implantation of the cup out of the true acetabulum. Zhao et al assessed the utility of digital preoperative templating in patients with Crowe Type 2 and 3 compared with a control group with other primary diagnoses and found significantly

lower predictability in dysplastic hip group but there was no significant difference in the femoral component size. The author concluded that the low accuracy for the predicting the acetabular cup might be a result of the difficulty in predicting the vertical hip center in patients with DDH.<sup>25</sup>

It has also been found that the accuracy of the templating procedure does not entirely depend upon the method of templating but is also determined by the efficiency and the experience of the physician<sup>26</sup>. In our study all surgeries and templating were performed by the same experienced surgeon.

Sershon R. et. also investigated the affects of BMI on accuracy of digital templating. Nevertheless, statistically significance can only be shown for the comparison of normal weight and over-weight people. However, this negative influence of obesity has not been confirmed statistically<sup>27</sup>.

## **CONCLUSION**

In conclusion, since the structural deformities of complex hip joint, prediction of the landmarks on x-ray for the digital templating is difficult also the fixation of the cup to the true acetabulum and maintain the exact vertical offset is challenge of the surgery. Because of these difficulties the prediction of the exact acetabular cup size in complex THA surgery is an complicated issue

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## FIGURES

### Figure-1



A: Preoperative digital templating of the inflamatur arthrodesis of right hip joint B: Measurements of templating C: THA of right hip

### Figure-2



A: Preoperative digital templating of left hip B: Measurements of templating C: THA of left hip with proximal femoral osteotomy

### Figure-3



A: Preoperative x-ray of right hip: Crowe type-3 B: Preoperative digital templating C: THA of right hip joint with femoral head osteograft.

## Chapter III



# Intraosseous Hemangioma of the Humerus Diaphysis

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## **Introduction**

Intraosseous hemangiomas are mostly localized in skull (80%) or vertebrae (30-50%). Involvement in long and flat bones is very rare. They are encountered as small lesions localized in metaphysis of long bones (1,2). Considering the rarity and variousity in radiological appearance, intraosseous hemangiomas of long and flat bones are hardly diagnosed. We described an intraosseous hemangioma case localized in humerus diaphysis and treated surgically.

## **Case Report**

An 8-year-old girl with an anamnesis of pain for the last 6 months had tenderness localized in middle right arm. An intramedullary tumor lesion of right humerus with an approximate size of 78x19 mm and leading cortical thinning without pathological fracture and soft tissue involvement were detected in the radiographic studies (Fig.1).



Fig.1

Fibrous dysplasia was thought in the first plane as a prediagnosis. Under the general anaesthesia a cortical window was opened to the humerus and frozen material was sent for biopsy (Fig.2).



Fig.2

Curettage and grafting were performed after having the frozen material as benign vascular lesion (Fig.3).



(Fig.3)

The definitive pathological diagnosis came as intraosseous hemangioma. There was no recurrence in the postoperative 6th month. There was also no other pathology in clinical examination. Periodical follow-up was planned.

### **Discussion**

The etiology of hemangioma is not definite. Some authors like Godanich and Capanacci considered the lesion as hamartoma, on the other hand some other like Mulliken counted it as vascular lesion (3). Hemangiomas of the bone are very rare and make up 0,5-1% of bone tumors (2,4). Jaffe (5) commented concerning with these tumors as “It is only rarely that one encounters a hemangioma which has originated within a bone other than a vertebra or a calvarial bone.” And Wilner [6] reported that “The radiologist is unlikely indeed to encounter a primary hemangioma of long bone.” Due to the fact that it is seen rarely, a hemangioma of the skeleton might have hardships about diagnosis for both pathologist and radiologist. These tumors are generally asymptomatic and possess female predominance (4). They are seen rarely in patients below 10 years old and the ones over 60 years old. Occasionally even if they are asymptomatic clinically, they might present with pain stemming from growth of the tumor and pathological fracture. Involvement of long tubular bones are rare. The most commonly affected site is metaphysis. That’s why radiological and histological diagnosis of a lesion localized in

diaphysis is difficult (1,3). Hemangiomas in long bones such as the femur and humerus, generally come up with a “soap-bubble” appearance so that it may be misdiagnosed as fibrous dysplasia, giant cell tumor, chondrosarcoma and aneurysmal bone cyst. Sarcomas, metastases and multiple myeloma are kept in mind in differential diagnosis (2,4,7). Histopathological study might be carried out in suspicious lesions as tru-cut biopsy or open surgical biopsy. The treatment of intraosseous hemangiomas is concerning with the local symptoms. Degredation might happen as the bone hemangioma grows and vascular tissue might be replaced by fibrous tissue. That’s why patients with no symptoms must be followed-up and aggressive treatment should be avoided (2,8). The treatment in hemangioma of a long bone is related with the involvement and the extension of the lesion. A localized and well bordered lesions are easy to treat with intralesional curettage and grafting or radiotherapy and cement injection. The most significant complication of the surgery is the bleeding (2,9). In our case, there was no local recurrence of hemangioma for 6 months follow-up. However, a longer follow-up period is needed to validate the success of the operation.

### **Conclusion**

Consequently, diagnosis of the hemangioma of the bones is very challenging even if they do not possess a critical importance in terms of health. These tumors must be considered in differential diagnosis of bone tumors with a high suspicion index. A multidisciplinary approach among pathologist, radiologis, and surgeon must be followed so as to make a correct diagnosis due to the fact that they are rare, and their radiological appearance and confusing histopathological pattern make it difficult to easily diagnose them.

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## **Chapter IV**

# Polycystic Ovary Syndrome Accompanying Medical Disorders and Long Term Health Risks

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Polycystic Ovary Syndrome with its reproductive, metabolic, and psychological effects is a significant community health problem (1). However, during the diagnosis and treatment planning for the complaints, the heterogeneous nature of the disease is generally ignored, and there is often insufficient consultation on the comorbidities and long-term risks of the disease. Although there is a marked clinical variation in the course of the disease throughout life, medical problems associated with PCOS may reappear with additional comorbidities.

Today, while many associations and groups are still trying to define and interpret the disease from their perspectives, the necessity to make new modifications in the diagnostic criteria and management of PCOS has re-emerged. The most recent of them is the '2018 International evidence-based PCOS assessment and management guide' (2018 PCOS Guide)', which was partnered with the European Society of Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM) (2).

## **Pathophysiology**

PCOS is thought to be a multi-systemic disease with genetic transmission, although Mendelian transmission could not be demonstrated (3). Identification of high levels of glucose metabolism disorders in PCOS cases, documenting the presence of insulin resistance to some extent in almost all PCOS cases and affecting androgen synthesis directly through the theca cells suggest that insulin resistance plays a central role in pathophysiology (4). Also, the ovaries of women with PCOS are thought to be more sensitive to insulin-induced androgen synthesis (5). The integral part of the disease is suggested to be hyperandrogenism. However, it is not clear exactly which pathways insulin resistance causes ovulatory dysfunction and hyperandrogenemia. One of the most suggested views

is that hyperinsulinemia caused by insulin resistance affects ovarian steroidogenesis and causes hyperandrogenism and thus ovulatory dysfunction. Insulin resistance in PCOS is thought to be the result of post-receptor defects. Combination of these defects with other factors may cause different phenotypes

In any case, both insulin resistance and hyperandrogenemia, and the presence of both put patients at high risk for metabolic disorders and cardiovascular diseases.

### **A. Disorders of glucose metabolism**

In any case, it is a known fact that the prevalence of glucose metabolism disorders increases in PCOS cases. However, documenting insulin resistance in the clinic is not always easy. For this purpose, the gold standard assays are only hyperinsulinemic-euglycemic clamp test, steady-state plasma glucose, or insulin suppression test. Routine tests, such as the oral "homeostasis model assessment model of insulin resistance" (HOMA-IR), are not reliable for measuring insulin resistance (6).

Although its application is not easy in routine, studies with euglycemic clamp test have documented that there is some degree of insulin resistance in both weak and obese PCOS patients (7). Although the risk of diabetes mellitus (DM) is known to be high in PCOS patients, this risk can sometimes be overlooked, especially in young patients in the clinic. However, beta-cell dysfunction has been shown to occur even in the adolescent group (8). When all the cases were considered, there were also researchers who reported that the probability of encountering the undiagnosed could reach up to 10%. In general, a woman diagnosed with PCOS has been reported to have an approximately 4-fold increased risk for Type2 DM after pairing with age and BMI (9). In systematic reviews, the prevalence of IGT and DM2 is high in PCOS patients independent of obesity and is seen at an earlier age (10).

Also, even if screening for DM2 is recommended in PCOS cases, which test (fasting blood glucose, OGTT or HbA1c) and how often it will be carried on remains to be discussed. Whether all PCOS cases will be screened or if additional risk factors (ethnicity, BMI, GDM history, family history) will be tested is another matter of debate. HbA1C, fasting blood sugar, 2nd-hour postprandial blood sugar, insulin resistance, triglyceride levels, SHBG levels, and basal BMI are the best predictors of DM2 development. Unfortunately, suggestions about which group should be screened are inadequate (11,15). However, it is known that Asians and obese patients are in a high-risk group. Of course, the frequency of follow-up in the general

population is recommended to be at least three years, although it varies with the assessment of additional risk factors. Although there is no absolute recommended method for an optimal screening test, HbA1C, fasting blood sugar, or OGTT can be used for this purpose. The recommendations of the associations on this subject may vary. For example, in 2018 ACOG 'Practice Bulletin, it is recommended to perform DM2 and impaired glucose tolerance screening with 75 g OGTT in each case diagnosed with PCOS (13). Screening is not recommended for insulin resistance. Also, it should be kept in mind that metabolic syndrome may be as frequent as 30% in PCOS cases (14)

According to the 2018 PCOS guideline, more selective recommendations are made for screening (2). These recommendations can be summarized as follows:

- All patients with PCOS should undergo basal glycemic control, and assessment should be continued every 1-3 years in cases with additional risk factors.

- Gestational diabetes, impaired glucose tolerance, and DM2 prevalence increase in all PCOS cases regardless of age.

- 75 g OGTT, FBS or HbA1C may be used for glycemic control. 75 gr OGTT is recommended in high-risk PCOS cases. High risk is defined as BMI greater than 25 kg / m<sup>2</sup>; Asian people whose BMI is higher than 23 kg / m<sup>2</sup>; those with impaired glucose tolerance, impaired fasting glucose, or a history of GDM; Cases with familial type 2 DM or HT history or high - risk ethnic group. It is known that DM2 risk is higher in Asian and American PCOS cases compared to Europeans. In conclusion, 75 g OGTT is not recommended in the first evaluation of PCOS cases with no additional risk factors.

- 75 gr OGTT should be administered to all pregnant women who have been treated in the periconceptional period or fertility treatment. If not done in the preconceptional period before the 20th week and 24-28. OGTT should be recommended to all cases in the postnatal week.

### **B.CVS diseases**

However, considering the strong relationship between PCOS and insulin resistance, it is clear that metabolic syndrome and its components (diabetes, hypertension, dyslipidemia) should be evaluated in all PCOS cases (15).

Whether or not the prevalence of the cardiovascular disease in PCOS cases has increased has yet to be discussed. For example, in an old Mayo Clinic study, there was no increase in myocardial infarction and other cardiac diseases in PCOS cases during long-term follow-up

(mean 23 years) (16). However, the lack of difference in the prevalence of DM 2 in this study raises questions about the sensitivity of the definition of PCOS group. In the large series, the Nurse Health Study is, the presence of irregular menstruation increased the risk of myocardial infarction (17). In the literature, there is no prospective study showing that the prevalence of the cardiovascular disease is increased in PCOS cases. It should be noted that inconsistent results in the literature may be related to heterogeneous patient groups and PCOS definitions. Therefore, although there is insufficient evidence to make a definitive judgment, a more sensitive evaluation is made, especially in cases with obese, hyperandrogenemia, and metabolic syndrome components. Although there are no recommendations for routine markers of cardiovascular disease, “carotid intima-media thickness” and aortic calcification are still under investigation. In ACOG 'Practice Bulletin' of 2018, it is emphasized that BMI, fasting lipid profile, and metabolic syndrome components should be evaluated in all PCOS cases.

Regardless of PCOS, cardiovascular diseases are among the leading causes of female deaths worldwide. Although cardiovascular diseases occur mostly in late reproductive and postmenopausal periods, risk factors begin to affect patients from a young age and increase cumulatively. Therefore, evaluation of well-defined cardiovascular risk factors (ethnicity, weight, BMI, waist circumference, lipid profiles, blood pressure, glucose levels, and physical activity status) in PCOS cases may be critical in the follow-up of these patients (18).

All PCOS cases should be evaluated in terms of cardiovascular risk factors and global cardiovascular risk.

Cases with obesity, smoking, dyslipidemia, hypertension, impaired glucose intolerance, decreased physical activity should be considered as high risk.

- Blood pressure of all PCOS cases should be checked annually, especially in high-risk situations.

- All PCOS cases should be monitored for weight gain and changes. The frequency of follow-up should be individualized at each visit with the most prolonged intervals of 6-12 months.

- BMI and waist circumference should be performed by WHO guideline according to ethnic and adolescent change intervals. Monitor and waist circumference measurements should be performed mainly for Asian and high-risk ethnic groups.

Lipid profile of patients with weight and obese PCOS should be checked regardless of age. Follow-up frequency values should be determined according to the presence of hyperlipidemia and cardiovascular risk factors.

-The differences between the facilities should not be forgotten.

Given all this information, it is evident that more sensitive and reliable methods to determine the risk of cardiovascular disease in PCOS are needed, and therefore, prospective studies on a more homogeneous patient group are required. Until such a screening test is identified, it would be appropriate to evaluate all patients as discussed above.

### **C. Obstructive Sleep Apnea (OSA)**

OSA is more common in PCOS independent of obesity (19). Hyperandrogenism may contribute to this condition (20). However, the available data suggest that screening should only be performed to identify and reduce symptoms (snoring, waking up from sleep, mood changes due to fatigue and daytime sleepiness). There is insufficient evidence to show the benefit of OSA treatment to cardiometabolic risk parameters in the general population and PCOS cases. For this purpose, the Berlin questionnaire can be used, and positive cases can be referred to the specialist. A positive test alone does not necessarily mean treatment, but it may be considered to refer the patient for further examination (2).

### **D. Postmenopausal problems**

We do not have sufficient data on the natural history of PCOS and its variation with age, according to phenotypes. The diagnosis of PCOS is made based on the Rotterdam criteria; however, changes in diagnostic tests and phenotype with age lead to controversy about the diagnosis, especially in the menopausal group. With advancing age, there are changes in all three diagnostic criteria (21). For example, ovarian volume and follicle number decrease with age. Although this decrease was reported to be less in PCOS cases compared to the control groups, there were no standardized values for age. In PCOS cases, menstrual cycles are more regulated with age, but ovulation decreases physiologically in the perimenopausal period. However, PCOS was found to be associated with late menopause (22). Although androgen levels are higher in postmenopausal PCOS cases compared to controls, androgen tests are not sensitive enough in low androgen levels, especially in the postmenopausal period (23).

- Postmenopausal PCOS diagnosis can be considered if there is a history of PCOS in the reproductive period.

- Postmenopausal PCOS persistence should be evaluated with the presence of persistent hyperandrogenemia.

- In case of new onset, severe or increased hyperandrogenemia, androgen-secreting tumors, and ovarian hyperthecosis should be ruled out.

In conclusion, there is no PCOS phenotype reported after menopause (24). In this context, follow-up studies on PCOS persistence and resolution are needed. Besides, if the risk factors of postmenopausal PCOS patients are considered to be combined with age, it should be remembered that metabolic risks should be evaluated

### **E. Endometrial Cancer**

Type 1 endometrial cancers are 2-6 times more common in PCOS cases and are mostly observed in the premenopausal period (25). Prolonged exposure to estrogen due to anovulation of the endometrium plays a significant role in the pathophysiology, but obesity, infertility, DM2, and the presence of metabolic syndrome lead to increased risk. Moreover, endometrial progesterone resistance may be present in PCOS cases (26).

Routine screening is not recommended, but evaluation by transvaginal ultrasonography and / or endometrial biopsy is recommended in patients with prolonged amenorrhea, persistent endometrial thickness, abnormal bleeding, or additional risk factors such as excess weight (26).

The optimal protection method could not be determined. In oligoamenorrheic cases with a cycle of more than 90 days, COC and progestin therapy will be beneficial. However, Metformin has no protective effect on endometrial cancer (27). Clomiphene studies have been shown to cause a slight increase in risk, although not sufficiently strong (28). Although the data related to letrozole is insufficient, it is predicted that it may reduce the risk of hormone-related cancer by considering its use in breast cancer (27). In conclusion, although the pathophysiology of PCOS cases is complex and multifactorial, it is essential to be aware of the increased risk of endometrial cancer.

### **F. Emotional Goodness**

The physical, social and emotional effects of chronic diseases and treatment process on patients should not be ignored. Correction of health-related poor quality of life with individualized approaches considering personal priorities is part of the treatment process. The effects of PCOS associated with symptoms such as menstrual irregularities, obesity, hirsutism, acne and infertility on the quality of

life can be evaluated with particular questionnaires (Polycystic ovary syndromic questionnaire (PCOSQ) - (MPCOSQ)) (29). It should be kept in mind that PCOS has a high prevalence of anxiety and depressive disorders, especially in adolescents. At the time of diagnosis, patients should be routinely screened in this respect and referred for further evaluation if necessary. The optimal range of assessment for anxiety and depressive disorders could not be determined. Symptoms can be made by regional sources or by questionnaires, followed by a few initial questions questioning depressive and anxiety disorders (Generalized Anxiety Disorder Scale (GAD7)) (29). It should be noted that agents may increase PCOS symptoms, such as obesity, and PCOS symptoms (e.g., obesity, infertility, hirsutism), if pharmacological treatment is considered appropriate, and may increase anxiety and depressive symptoms. Psychosexual disorders which may be caused by depression, negative body perception, and low self-confidence are another vital health problem. Patients who are thought to have psychosexual dysfunction may be referred to the Female Sexual Function Index (FSFI) (Arizona Sexual Experience Scale (ASEX)) by referring to specified questionnaires (30). Achieving hirsutism, obesity, and menstrual regulation will positively affect the psychosexual quality of life of the patients. It should be noted that negative body perception is observed more frequently in PCOS cases (31). However, eating disorders are more common in these patients. Questionnaires may evaluate suspected cases and refer to as necessary (Sick, Control, One Stone, Fat, Food (SCOFF)) (32).

As a result, PCOS is a chronic disease and may experience different effects of the disease during life. The multidisciplinary approach will improve the quality of being associated with the patient's health. At the same time, comprehensive, evidence-based training of patients about the biopsychosocial effects of the disease is essential (2).

### **Result**

PCOS is the most common endocrinopathy in the reproductive age (1). However, reproductive, metabolic, systemic, or psychological effects may come into prominence separately in different periods of life. Although the comorbidities of PCOS are mostly known, the algorithms related to optimal screening, total risk assessment, and clinical management are still controversial for comorbidities in this patient group.

In this sense, the 2018 PCOS guideline will guide clinicians and enable multidisciplinary evaluation of additional comorbidities that

are ignored in addition to the dominant complaint. This guide focuses explicitly on different comorbidities and long-term risks. It can provide standardization in the long-term multidisciplinary management of these cases with practical suggestions.

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# Chapter V



# Clinical Importance of Persistent Cervical HPV Infection

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Well-designed cervical cancer screening programs allowed us to reduce the incidence of cervical cancer, which is one the leading cause of women cancer deaths worldwide. One important to step towards eradicating cervical cancer is development of HPV vaccines because infection with high risk oncogenic Human papillomavirus (HPV) underlies almost in all cervical cancer cases. Therefore, according to this relationship of cancer development, HPV is the most prominent virus among all cancer viruses. Besides, HPV is also responsible for considerable amount of anal and oropharyngeal cancers (1). Despite the decreasing trend in cervical carcinoma, incidence of anal cancer however have been increasing especially over the last two decade (2). One reason for this is the fact that there have been no universally applicable screening programs for such cancers. Understanding the natural history of cervical HPV infection will eventually lead to development of molecular screening

Persistence of high risk HPV infection may yield to cancer formation. Worldwide estimation states that nealy 5 percent of all cancers is related with HPV infection (3). Therefore, HPV is the most dangerous oncovirus. Oncoviruses were first discovered in the beginning of 1900s. Ellerman and Bang reported for the first time that some "filterable agents" are related with lymphomas in chickens. Peyton Rous extended these findings and discovered a virus (Rous sarcoma virus) that cause solid tumors in chickens (4,5). Interestingly, this finding initiated a great debate because at that time the consensus states that cancer development is an endogenous process and an viral origin was fictitious. Therefore, he was criticized with the claim that "this can't be cancer, because you know its cause" (6-R06). Ironically, this causality later resulted in a Nobel Prize in 1966. Until 1960s the mechanism of this causality remained enigmatic. The first clues

however, indicated that an extra gene in the Rous sarcoma virus (RSV) is required for malign transformation but not for viral replication. This finding showed that replication of the virus and oncogenic transformation might be separable processes of RSV (6). Therefore, these genes that are involved in malign processes are started to be called as “viral oncogenes” for the first time. Another groundbreaking finding was later came from Stehelin, Varmus, Bishop, and Vogt when they reported that homologous sequences of the transforming gene in RSV genome was also found in several normal avian DNAs (7). But the question of “Why does RSV carry a gene causing cancer that is not required for viral replication and did it come from normal DNA?” was still unanswered at those times. However, this result induced scientists to consider the concept of “proto-oncogene”. Eventually, “c-src” was documented as the first discovered proto-oncogene in humans and Bishop and Varmus later earned 1989 Nobel Prize in 1989 (6). Today it is known that the cancer forming viral oncogene of Rous sarcoma virus (*v-Src*) had been captured from proto-oncogene (*c-src*) from a normal cells’ DNA.

Papillomaviruses are small DNA viruses. There are more than 150 defined types of HPV. Oncogenic genotypes are related with several cancer types (cervical, anal, vaginal, vulvar, and penile cancers and the cancer of the oropharynx). In 1976, Harald zur Hausen suggested that cervical cancer is a result of papillomaviruses infection of the cervix (8). In the following years, his team found a particular integration pattern of HPVs and documented selective expression of two genes (E6 and E7) in cervical cancer cells (9). The most important implication of this finding was the possibility of vaccines against HPV. Harald zur Hausen shared the Nobel Prize in 2008 with Luc Montagnier and Françoise Barré-Sinoussi, who defined the human immunodeficiency virus. Today eight genes were defined in the HPV genome codes. The primary HPV oncoproteins are E6 and E7. E6 and E7 proteins targets and result in degradation p53 and pRB, respectively. Inhibition of p53 and pRB causes blockage of apoptosis and result in abnormal cell-cycle, initiating the progression to cancer. (10)

The most important step for oncogenic transformation after infection with high risk HPV types is the persistence of the virus. Although clearance is common in young women, several risk factors can be associated with persistence. Besides, viral load and genotype are the main cofactors for progression. In fact persistence of HPV infection requires a specific kind of involvement; basal cells are needed to be infected because basal cells have stem cell-like features (11). This kind of infection is mostly seen in high risk genotypes.

Another distinct feature of high risk HPV genotypes is the fact that they cause carcinogenesis generally in specific areas such as transformation zone and anorectal junction (12). Although the driving mechanism in carcinogenesis is related with E6 and E7 proteins and both low risk and high risk types express these proteins, it is the insufficiency in low risk types that differ to trigger the development of preneoplastic lesions (13). In order to achieve this trigger, HPV should have to evade from host immune system. This evasion is critical for persistence. One important mechanism is the non-lytic nature of the HPV infection, which assures that inflammatory signaling is prevented. Another mechanism is inhibition of Langerhans cells (LC), limiting activation of adherence molecules and modulation of inflammatory signaling pathways (14). Besides from their effect in cell cycle, E6 and E7 proteins also function in inhibiting LCs.

Naturally, soon after a sexual contact with an infected sexual partner a new infection occurs. In most of these cases HPV DNA become detectable in the first year of this infection (15). Therefore, a rise in prevalence is seen among the young ages in which first sexual contact occur. This age can change from region to region according to the onset age of sexual contact. Some researchers reported a second rise in postmenopozal ages, however the exact mechanism of this peak is not clear (16). It was clearly documented in of the first prospective studies that the acquisition rate is higher in younger ages after first sexual contact (cumulative incidence of 0.42 in women aged 15-19 years in contrast to a cumulative incidence of 0.12 in women aged >44 years)(17). It is evident that risk is increased in women with multipartners when compared to those having one sexual partner (18).

Once a cervical HPV infection is acquired, in half of the cases HPV infections clear within 6 months (19). During follow-up, most of the cases clear after 2 years (20). Since HPV does not make any viremia or lytic infections, the most important immune mechanism for this clearance is apparently cell mediated immune response (21). Studies have shown several risk factors associated with lower clearance rates: lower absolute number of endocervical LCs, less *Lactobacillus* spp. in the vaginal microbiome, and a high incidence of bacterial vaginosis. (21-23). It has been shown that antibodies against HPV are found in only limited number of cases, indicating a limited role of humoral immunity for these cases (24). Similarly, a systematic review showed that seroprevalence against HPV16 ranges between 6.2%-45.5% and this has only a modest protection for HPV reinfection (25). Therefore, it is estimated that seroprevalence is not an important determinant of HPV persistence or clearance. Viral genetic variation, besides from the HPV genotype also plays a role in

different patterns of viral persistence. As definition a new genotype is not defined unless more than 10% difference is observed from other genotypes in the L1 sequence (26).

Some patients were found to be HPV positive after HPV clearance was observed. Sometimes the recurrent infection is with the same HPV genotype (27). Therefore one can speculate that several other risk factors for recurrence predisposes some women to reinfection with HPV. One interesting explanation dormant HPV presence in the basal epithelial layer or re-inoculation (28). This kind of latent infection is kept under control by a suppressive immune environment and the viruses are kept in low copy numbers that allows the virus to escape from detection. Several factors including hormonal changes (i.e. menopause) that induce a relative immunosuppressive situations may cause increased viral replication (29). There has been no crystal clear evidence to account the real role of reinfection in HPV recurrence. One intriguing detail in recurrent cases is the possibility that some of these women that recurrence occurs with a different HPV genotype do not have any active sexual life. Therefore, autoinoculation seems to be another explanation for these cases. The most probable source for HPV autoinoculation would be the anal canal due to its close regional proximity to cervix. A similar autoinoculation mechanism was also argued for beta-HPVs, but no prospective studies for alpha HPVs were available (30). It has been speculated that the risk of reinfection in cervix can be related with concomitant anal HPV infection (31).

Regardless of the underlying mechanism for persistence in HPV infection, these cases carry a higher risk for cervical cancer development (32). Since many screening programs implement a HPV re-test after first screening with a HPV-positive but cytology negative result, persistence is generally checked at this time. The optimal definition of time interval for persistence is yet to be defined. The most important determinant of HPV persistence at the time of first infection is the HPV genotype and viral load (33). Age also may also affect HPV clearance. Concomitant infection however, seems not to affect clearance rate (34). Development of high grade lesions or cancer can occur as early as 5 years apart from persistence (35). Other risk factors that are associated with cervical cancer development (smoking, multiparity, oral contraceptives) should also increase the risk of HPV persistence in order to affect neoplastic differentiation. Analysis of a large cohort of women documented that parity and long term contraceptive use (more than 15 years) significantly increased the CIN3 risk (36). The above-mentioned factors along with immune conditions should be kept in mind in persistent HPV cases because all

of them can be regarded as risk factor not only for persistent infection but also for cancer development.

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## **Chapter VI**

# **Violence Committed by Woman Against Herself in Terms of Social Gender**

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## **Introduction**

We can define violence in general as “any action that harms others both physically and psychologically as well as economically and culturally”. There are many types of violence against women, including physical, sexual, psychological/emotional and economic. According to the definition of WHO, violence against women is defined as 'any behavior that is based on gender, that hurts and harms women, that may result in physical, sexual, or mental damage, that leads to pressurizing them within the society or in their private life and restriction of their freedom arbitrarily' (1,2,3).

The definitions about violence are generally based on interpersonal relations. However, within the context of violence, it is possible to talk about self-directed and collective forms of violence besides interpersonal violence. When we look at violence especially in terms of social gender, perhaps the violence we have never dealt with or talked about is the violence the women commit against themselves as social gender.

In the concept of social gender, it is a known fact that femininity and masculinity in general are defined as social/cultural/historical differences besides biological differences and are built and changed as learned roles and behaviors.

The use of violence by men is also related to the tasks determined by the society and the wishes and desires they created on men. Throughout history, the existence of women in societies has passed and still passes through men's satisfaction.

The women have always been nominated with making the men satisfied and happy. For this reason, in order for the men to be satisfied sexually, women must enter any sexual intercourse he desires

without rejection. The women must try all kinds of ways for the men not to go out and to be satisfied. They do not hesitate to resort to ways such as having vaginoplasty to ensure the men have more pleasure and even re-presenting herself to the men by having hymenoplasty. Because it is given culturally that the conditions of being women are through the satisfaction of men. Again, what is told to them from their childhood is to look after and satisfy their men, and that they do not have the option and right to refuse.

### **Social Gender**

Whether the origins of social gender concepts are based on biological and physiological structural differences between men and women or a psychological and sociocultural structure has been discussed from the first stage and is still being discussed. In the 1970s, the first debate began, and from the 1990s onwards, social gender increasingly became and still continues to be the subject of studies (4). There are those who argue that biological differences are expressed in terms of gender and sociocultural differences in terms of social gender, as well as those who argue that differences are shaped both socioculturally and biologically. Social gender has also been used to explain the relationships between the genders. The oppression of women, the fact that they are not accepted as individuals and the formation of a male-dominated picture throughout the world is the result of social structuring. The origins of men's power against women are very old and this superiority was supported and is being supported in terms of religion and philosophy (5,6,7).

### **Violence**

Violence is defined as an act or restriction applied with the aim of harming an individual, and a mistreatment by force. Violence is a social problem that may exist in all areas of life (8,9).

According to the definition of WHO, violence against women is defined as 'any behavior that is based on gender, that hurts and harms women, that may result in physical, sexual, or mental damage, that leads to pressurizing them within the society or in their private life and restriction of their freedom arbitrarily' (10,11). Violence poses a serious threat to women's health in terms of physical health problems and mental health problems. It is reported that psychological and behavioral problems such as depression, excessive alcohol use, panic anxiety, suicidal behavior have also been encountered in women who have been subjected to any form of violence (8,11).

## **Violence Committed by Woman Against Herself in Terms of Social Gender;**

Body; other disciplines as well as scientific branches such as philosophy, psychology and anthropology are effective on the body. Religions, ideological formations and political orders tend to control the body. It is the body that the individual most easily controls or strives to control. There are behaviors expected from men and women in social life. For this reason, we can say that the body's physical perception and the physical perception of the society have developed as a result of the reactions created by the internalization of social habits. When we look at how individuals shape their bodies through social structures, previous experiences have an important role in adapting to social conditions. The body constitutes the most important part of an individual's self-perception, personality and identity. Generally, people have an impact on others with their appearance. This is related to the way the body is used. There is also a body structure that is formed in the mind of the person who knows that s/he defines himself/herself with the body structure of others. Whether s/he is satisfied with this body structure affects his/her self-value. The person who realizes his/her physical life through his/her physical perceptions also realizes his/her mental and psychological life through his/her physical perception. In other words, how one perceives himself is closely related to his body. The body also determines the health and beauty understanding of persons through sociocultural approaches. Therefore, the physical appearance has been accepted as a norm of beauty that is desired to be achieved (12,13,14,15,16).

Women in a social understanding dominated by the idea that women will be beautiful only when they are very thin will do extreme sports and diet in order to be and stay slim, and if they cannot achieve their targets through these ways, they will have surgical procedures for this purpose. Every action they take will put their lives at risk as a serious violence against themselves (17).

When we look at virginity from a patriarchal point of view as a patriarchal society, virginity is the precondition for the obsession of domination that men desire to establish on women. Being the first is the consolidation of the dominion in the masculine ego (18). Although there have been some changes recently, virginity has an important place in our society. While virginity includes first dominion, nobody touched before me, first I had her, she was with me first, etc. ideas for men, it includes I became yours first, nobody other than you touched me, I kept myself for you, I am pure and clean, etc. ideas for women. All of these beliefs and modes of thought are supported culturally, and the virgins are defined as girls and non-virgins are defined as women,

and thus social pressure and discrimination come into prominence. Because of these social pressures and cultural factors, the first partnerships have always played an important role.

In patriarchal societies where virginity is considered an honor, women undergo a hymenoplasty operation in order not to lose their chances of marriage. It has been recognized that there is a social importance as an assurance of women especially in conservative societies and that it should be known by gynecologists and it is a health service (19,20). Virginity, which has an important place in the culture of the society where grown, has the meaning of presenting herself for women and having dominion for men and has an important place in partnerships. Under these circumstances, the hymenoplasty for the elimination of a social problem and which is accepted as the life assurance of the women is today a way of re-presenting themselves to their spouses during their marriage anniversaries and giving them the taste of first partnership.

Vagina aesthetics; It is a method that has been frequently performed also in our country in recent years as a way to eliminate the self-confidence problems and sexual function problems that have arisen with the loss of the aesthetics and expansion of the vagina over time. In Bergey's book "Ways of Seeing", men are like they behave and women are like they seem, men watch women, and women watch that they are watched, and this situation determines not only the relationships between men and women, but also women's relations with themselves. The woman who knows that she is being watched always wants to make herself being watched by men as admired and worth for watching, and she tries every way for this. Vagina aesthetics surgeries first started in the USA and EU and in recent years they have become a big trend in our country. On the other hand, in our country, sexual dysfunctions among spouses are more common reasons of such surgeries. Women are more concerned with the happiness of their husbands (men) than with their own happiness. Thus, the woman fulfills the duty of making her man happy, the most important of her feminine roles as social gender. According to the result of a study published in Cumhuriyet Newspaper, 20% of the women in Turkey request vagina aesthetics (vaginoplasty, cliteroplasty, labioplasty) in order to eliminate the deformations in vaginal area (21,22,23). In recent procedures, applications with increased aesthetic concerns such as laser discoloration of the genital area, cliteroplasty and episiotomy have increased.

The culture of a society includes norms or expectations about how men and women be, how they should behave, think and act within the society. Sexuality and sexual roles of men and women in society also

differ. With these thoughts, female circumcisions are applied in some communities, especially in order for men to achieve more satisfaction from sexual relations (24).

Female circumcisions; cutting of some part of clitoris (Type 1), the whole or part of clitoris and labia minors (Type 2), and in addition to labia minor and major, some part of vaginal orifice (Type 3) and external genital organ for the applications such as Piercing (Type 4), still continue to be applied in 29 countries although there is no health reason, due to religious requirements, giving more satisfaction to their husbands, protection of virginity, belief of establishing better marriage, and social acceptance and cleanliness, and there are 125 million circumcised women (25). This type of culturally applied violence is a situation which is not applied by women to themselves but accepted by them to be applied on them.

As a result, we can say that while sexuality should be the basic principle of being human and getting pleasure together for both men and women, women can sacrifice themselves or have themselves sacrificed for the pleasure of men. Women do not perceive these acts as violence against themselves. They perform the actions of womanhood and presenting themselves to their men and making them happy in the best way as they have learned in line with the culture they live in.

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## **Chapter VII**

# Endovascular Treatment in Leriche Syndrome

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## **Introduction:**

Leriche syndrome is characterized by the onset of marked gradual occlusion of the terminal aorta and/or bilateral iliac arteries, and is classically associated with a triad of symptoms comprising intermittent claudication, absent or diminished peripheral pulses, erectile dysfunction in man (1). Endovascular treatment of aortoiliac occlusive disease involving the aortic bifurcation is challenging. The gold standard is open surgery with patency rates up 90% at 5 years, but has considerable morbidity and mortality. Perioperative mortality of 1-3 % can be achieved. We reported a case of Leriche syndrome treated with EVT in a patient with high surgical risk.

## **Case Report:**

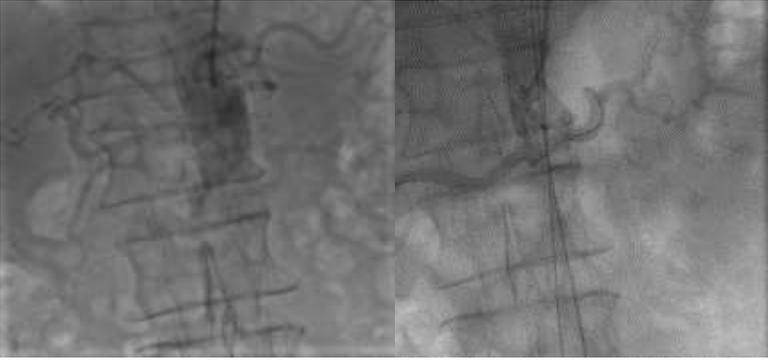
A 43-year-old man with a history of underwent abdominal surgery two times visited our hospital with intermittent claudication. Upon an examination, the bilateral common femoral arteries were not palpable. The patient's body mass index was 22.7 kg/m<sup>2</sup>, with the following laboratory data: hemoglobin 14.2 g/dl; serum creatinine 0.89 mg/dl (estimated GFR 60ml/min/1.80 m<sup>2</sup>). The ankle- brachial index (ABI) was very low on both sides (right:0.40, left:0.38), and severe bilateral limb artery stenosis and occlusion was suspected. A three-dimensional computed tomography (3D-CT) angiogram subsequently indicated bilateral AIOD (Figure 1).



*Figure 1*

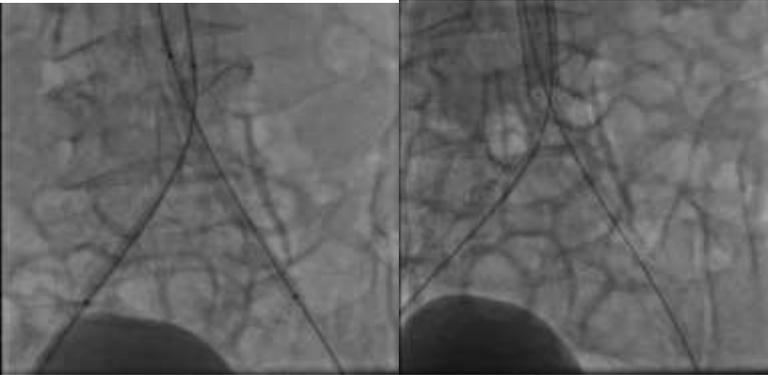
Coronary angiography showed normal coronary arteries. Although the patient first planned to undergo open surgery that in this case would carry high operative risks for underwent abdominal surgery about 2 years before so the adhesion of abdominal organs was suspected. In addition, the patient strongly refused to undergo open surgery. Therefore, we decided to perform EVT for Leriche syndrome.

We approached the occluding lesion from three points, including the bilateral femoral arteries using 6-F sheaths and the left brachial artery using a 4-F sheath. Heparin was administered intravenously at a dose of 5000 IU. The proximal fibrous cap of the occlusion site of terminal aorta was penetrated by using a multipurpose catheter and a 0.0035-inch radiofocus guidewire (GW) (Terumo Corp., Japan) (Figure 2a). Then the radiofocus GW was exchanged for a Treasure XS12 and crossed from the aorta. Another Treasure XS12 was advanced from the right femoral artery to the aorta (Figure 2b). The occluded segments of the bilateral iliac arteries were predilated with either of the 7.0 mm (80 mm) balloons (Figure 2c). An Optimed 18mm (80 mm) stent were inserted from right common iliac and advanced to the aorta. Also, an Optimed 7mm (80 mm) stent were inserted to left and right iliac artery and an Optimed 7mm (40 mm) stent were inserted the from right common iliac artery advanced to the right iliac artery (Figure 2d). The post-dilatation of the bilateral stents was performed simultaneously with two 5.0 mm balloons.



*Figure 2a*

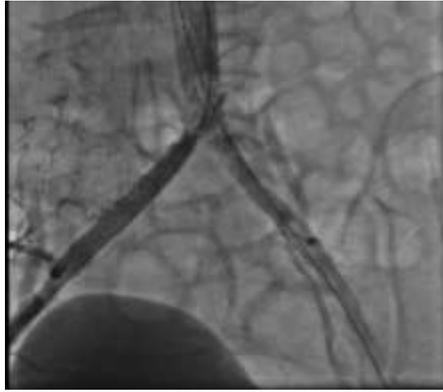
*Figure 2b*



*Figure 2c*

*Figure 2d*

The final angiogram showed no thromboembolism in the distal arteries (Figure 2e).



*Figure 2e*

The ABI dramatically improved (right 0.40 to 0.95 and left 0.38 to 0.96) and the patient was discharged on the 6<sup>th</sup> hospital day (4<sup>th</sup> day after EVT). Two months after the EVT procedure, the intermittent claudication improved completely. In addition, the ABI normalized (right: 1.03, left: 0.99), while CT showed good stent patency from the aorta to the bilateral iliac arteries and 3D-CT angiogram indicated full expansion of the stents (Figure 3). The patient's post EVT course has been uneventful for 18 months.



*Figure 3*

## Discussion

The TASC II guidelines in 2007 recommended surgical bypass for TASC C and D aorta-iliac lesions. It stated “Endovascular methods do not yield good enough results to justify them as primary treatment” for TASC D lesions, and “Open revascularization produces superior long term results”, and “Endovascular methods should only be used when there is a high risk associated with open repair” for TASC C lesions (2). However, major changes were made between the TASC I and TASC II classification, and more vascular surgeons are attempting to treat TASC C and TASC D lesions with EVT (2,3). Moreover, technical and device improvements have encouraged vascular surgeons to perform EVT for TASC C or TASC D aorta iliac-lesions during the last 10 years. The outcomes of EVT for TASC C and D aorta-iliac lesions were acceptable, with better technical success in TASC C lesions than in TASC D lesions (4).

One special type of AIOD is so-called “Leriche syndrome” which is characterized by marked gradual occlusion of the terminal aorta and/or bilateral iliac arteries (5). In general, surgical treatment has been recommended as a revascularization therapy for Leriche syndrome (6). Currently, the clinical outcome of EVT for Leriche syndrome remains unclear. The patency rate in AIOD patients undergoing open bypass surgery has been reported to 80-86% at five years and 72-79% at 10 years (7). The rate of primary patency in patients undergoing EVT is 64% at five years (8). A retrospective cohort study demonstrated that EVT for Leriche syndrome had a favorable outcome (9,10). A systematic review and meta-analysis demonstrated that the rates of both primary and secondary patency for open bypass are superior to EVT in patients with AIOD (11).

We reported a case of Leriche syndrome had treated with EVT. The patient had received abdominal surgery for acute abdomen at last two years two times that we believe this history of patients is due to mesenteric ischemia caused by undiagnosed AIOD disease. There was possibility of the adhesion of the abdominal organs. The adhesiolysis during reoperation was associated with an increase of sepsis incidence, intra-abdominal complications and wound infection, and longer hospital stay (12). Therefore, we decided to treat Leriche syndrome with EVT. We performed left brachial and bilateral femoral access using the Seldinger technique. The brachial approach offered a better pushability in complex endovascular procedures (13). In such this case distal embolization to calcified atherom plaque is may be one of the adverse complications. Primary stenting with the use of selfexpanding prostheses without predilation may reduce the risk of embolization (14). Distal embolization did not occur in this case;

however, it is important to take care of distal embolization. To prevent distal embolization, thrombus aspiration was done and dilatation after stenting was performed with small size balloons. The clinical course of this case was excellent.

### **Conclusion**

EVT may be a treatment option for Leriche syndrome with high technical success rates and minor complications occur.

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## Chapter VIII

# Characteristics of Patients Applying to the Emergency Department Due to Falling\*

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## **Introduction**

Trauma is an important source of morbidity and mortality among people who are younger than 45 years of age worldwide.<sup>(1, 2)</sup> When trauma is classified according to the mechanism of occurrence, falls have been shown to rank first in all age groups.<sup>(3-5)</sup> Falls are even more important among children and the elderly since they are common in those age groups; they cause serious injury, and they can be prevented with simple measures. Falls are an important source of mortality and morbidity in childhood. They constitute 25-34% of all emergency department admissions and 5.9% of childhood deaths in the United States. Many factors including age, the height of fall, cause of fall, type of surface fallen onto, and injured body parts may affect prognosis.<sup>(6-8)</sup>

Falls is the leading cause of trauma among the elderly, and declining physiological reserve, accelerating catabolic processes, increased prevalences of comorbidities, and higher rates of medication use not only increase the frequency of falls but also give rise to severe injury even after simple trauma.<sup>(9-11)</sup>

In this study, we aimed to review the demographic and clinical properties of patients admitted to the emergency department after falls in an attempt to make a contribution to the current literature.

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\* This study was presented as an oral presentation on June 28-30, 2019 at the 2<sup>nd</sup> International Hippocrates Congress on Medical and Health Sciences, İstanbul, Turkey.

## Materials and methods

### *Patient population and study design*

The study was carried out according to ethical standards of the 1975 Helsinki Declaration's Human Experiment Committee which was revised in 2000. Our study was retrospectively performed on 1054 patients admitted to the University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital Emergency Department between the dates of 1 January 2017- 1 January 2019. Age, gender, the height of fall, admission types, the month of trauma, cause of fall, pulse rate, mean arterial pressure (MAP), Glasgow Coma Scale (GCS), Injury Severity Score (ISS), injury site, and admission and mortality rates were recorded. Patient data were accessed through patient cards and hospital automation system. Patients with inaccessible or missing medical records were excluded.

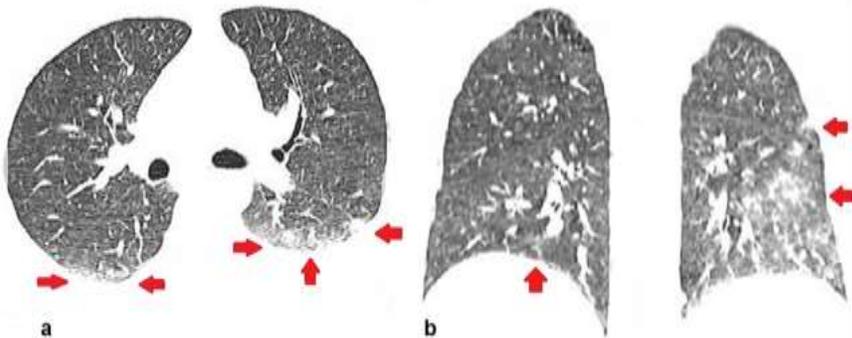
### *Statistical analysis*

Study data were analyzed using SPSS (Statistical Package for the Social Sciences for Windows version 22.0 SPSS Inc., Chicago, IL, U.S.A.). The distribution of quantitative data was tested with the Kolmogorov-Smirnov test. Quantitative nonparametric data were expressed as the median and interquartile range (IQR); qualitative data were expressed as number (n) and percentage (%). Comparison of quantitative data with qualitative data was performed using Mann-Whitney U and Kruskal-Wallis tests, and qualitative data were compared with each other using Pearson's Chi-Square test.  $P < 0.05$  was considered statistically significant.

## Results

The median age of the study population was 27 years (IQR=57), and the age range was 0-84 years. The height of the fall was zero meter in 13.1% of the patients; below 1 meter in 38.2%, and above 1 meter in 48.4%. The median age of the patients falling from the same height was the lowest and that of those falling from a height less than 1 meter was the highest ( $p < 0.05$ ). Males constitutes 55.7% of the study population, and the number of women falling from the same height was significantly higher ( $p < 0.05$ ). Fifty-two-point one percent of patients were transferred via ambulance; the rate of self-admission was higher among patients falling off the same height ( $p < 0.05$ ). Admissions occurred most commonly in summer (47.9%), with the incidence of falling from a height having increased in spring and summer ( $p < 0.05$ ). The most common cause of fall was slipping/stumbling/falls (50.4%), and the rate of falling off a height higher than 1 meter was higher among victims of work accidents and

Suicide committers ( $p < 0.05$ ). Patients falling from above a 1-meter height had higher pulse rate and ISS scores but significantly lower GCS and MAP ( $p < 0.05$ ). Trauma was most commonly localized to extremities (63.2%), followed by the head (28%). The rates of head, neck, thorax, abdomen, and the spinal injury was significantly higher among patients who fell off higher than 1 meter ( $p < 0.05$ ) (Figure 1). The admission rate was 24.2% and mortality rate 11.7%. The admission and mortality rates were significantly higher in patients falling off higher than 1 meter ( $p < 0.05$ ) (Table 1)



**Figure 1.** Axial (a) and coronal reformatted (b) Computed tomography images show pulmonary contusion; non-segmental, peripheral, parenchymal opacification in the lung (red arrows).

**Table 1.** Comparison of the height of fall and clinical properties

		Total (n=1054 )	Same height (n=141 )	1 meter > (n=403 )	1 meter < (n=510 )	<i>p</i>
Age, Median (IQR)		27 (57)	2 (7)	65 (49)	24 (21)	<0,001 <sup>a</sup> bc
Gender	Male, n(%)	587 (%55,7)	65 (%46,1 )	265 (%65,8 )	257 (%50,4 )	<0,001
	Female, n(%)	467 (%44,3)	76 (%53,9 )	138 (%34,2 )	253 (%49,6 )	
Admission type	Ambulance, n(%)	549 (%52,1)	13 (%9,2)	232 (%57,6 )	304 (%59,6 )	<0,001
	Self-admission, n(%)	505 (%47,9)	128 (%90,8 )	171 (%42,4 )	206 (%40,4 )	
Season	Summer, n(%)	374 (%35,5)	42 (%29,8 )	131 (%32,5 )	201 (%39,4 )	<0,001
	Autumn, n(%)	204 (%19,4)	22 (%15,6 )	102 (%25,3 )	80 (%15,7 )	
	Winter, n(%)	271 (%25,7)	39 (%27,7 )	88 (%21,8 )	144 (%28,2 )	
	Spring, n(%)	205 (%19,4)	38 (%15,6 )	82 (%25,3 )	85 (%15,7 )	
Cause	Work accident, n(%)	180 (%17,1)	0	36 (%8,9)	144 (%28,2 )	<0,001
	Suicide, n(%)	141 (%13,4)	0	0	141 (%27,6 )	
	Slipping/Fall/stumbli ng, n(%)	531 (%50,4)	73 (%51,8 )	299 (%74,2 )	159 (%31,2 )	
	Falling from lap, n(%)	62 (%5,9)	59 (%41,8 )	3 (%0,7)	0	
	Other*, n(%)	140 (%13,3)	9 (%6,4)	65 (%16,1 )	66 (%12,9 )	

Pulse rate, Median (IQR)		79 (27)	79 (23)	77 (14)	102 (42,5)	<0,001 <sup>b</sup> <sub>c</sub>
MAP, Median (IQR)		91,7 (31,7)	91 (28,7)	93,6 (14,7)	64,3 (10,8)	<0,001 <sup>b</sup> <sub>c</sub>
GCS, Median (IQR)		15 (0)	15 (0)	15 (0)	15 (2)	<0,001 <sup>b</sup> <sub>c</sub>
ISS, Median (IQR)		9 (16)	7 (10)	7 (5)	19 (20)	<0,001 <sup>b</sup> <sub>c</sub>
Injury site	Head, n(%)	295 (%28)	39 (%27,7)	33 (%8,2)	223 (%43,7)	<0,001
	Neck, n(%)	165 (%15,7)	10 (%7,1)	23 (%5,7)	132 (%25,9)	<0,001
	Thorax, n(%)	191 (%18,1)	1 (%0,7)	27 (%6,7)	163 (%32)	<0,001
	Abdomen, n(%)	59 (%5,6)	0	4 (%1)	55 (%10,8)	<0,001
	Ekstremiti, n(%)	666 (%63,2)	93 (%66)	318 (%78,9)	255 (%50)	<0,001
	Spinal, n(%)	202 (%19,2)	0	21 (%5,2)	181 (%35,5)	<0,001
Hospitalization		255 (%24,2)	18 (%12,8)	14 (%3,5)	223 (%43,7)	<0,001
Eksitus		123 (%11,7)	0	8 (%2)	115 (%22,5)	<0,001

IQR: Interquartile range, MAP: mean arterial pressure, GKS: Glasgow coma score, ISS: Injury severity score, (a: Same height-1<for lower than 1 meter p<0,05; b: Same height-1<for higher than 1 meter p<0,05; c: 1<for higher and lower than 1 meter 1 p<0,05), Other: Unknown reason.

The admission rate was significantly correlated to age, season, cause of fall, pulse rate, MAP, GCS, ISS, and trauma localization (p<0,05). It was not correlated to gender and admission type (p>0,05) (Table 2).

**Table 1.** Comparison of hospitalization and clinical properties

		Hospitalization		<i>P</i>
		Yes (n=255)	No (n=799)	
Age, Median (IQR)		23 (20)	28 (59)	<0 ,001
Gender	Male, n(%)	154 (%60,4)	433 (%54,2)	0,0 83
	Female, n(%)	101 (%39,6)	366 (%45,8)	
Admission type	Ambulance, n(%)	130 (%51)	419 (%52,4)	0,6 84
	Self-admission, n(%)	125 (%49)	380 (%47,6)	
Season	Summer, n(%)	124 (%48,6)	250 (%31,3)	<0 ,001
	Autumn, n(%)	31 (%12,2)	173 (%21,7)	
	Winter, n(%)	46 (%18)	225 (%28,2)	
	Spring, n(%)	54 (%21,2)	151 (%18,9)	
Cause	Work accident, n(%)	81 (%31,8)	99 (%12,4)	<0 ,001
	Suicide, n(%)	45 (%17,6)	96 (%12)	
	Slipping/Fall/stumbling, n(%)	86 (%33,7)	445 (%55,7)	
	Falling from lap, n(%)	12 (%4,7)	50 (%6,3)	
	Other, n(%)	31 (%12,2)	109 (%13,6)	
Pulse rate, Median (IQR)		79 (27)	78 (22)	<0 ,001
MAP, Median (IQR)		91,7 (31,7)	89,7 (35,7)	0,0 31
GCS, Median (IQR)		14 (3)	15 (0)	<0 ,001
ISS, Median (IQR)		28 (9)	7 (7)	<0 ,001
Injury site	Head, n(%)	134	161	<0

		(%52,5)	(%20,2)	,001
	Neck, n(%)	77 (%30,2)	88 (%11)	<0,001
	Thorax, n(%)	146 (%57,3)	45 (%5,6)	<0,001
	Abdomen, n(%)	35 (%13,7)	24 (%3)	<0,001
	Ekstremiti, n(%)	138 (%54,1)	528 (%66,1)	0,001
	Spinal, n(%)	96 (%37,6)	106 (%13,3)	<0,001

IQR: İnterquantile range, MAP: mean arterial pressure, GKS: Glasgow coma score, ISS: Injury severity score, Other: Unknown reason.

The mortality rate was significantly correlated to age, gender, season, cause of fall, pulse rate, MAP, GCS, ISS, and trauma localization ( $p < 0,05$ ) but not to admission type ( $p > 0,05$ ) (Table 3).

**Table 3.** Comparison of mortality and clinical properties

		Mortality		<i>P</i>
		Survive (n=931)	Eksitus (n=123)	
Age, Median (IQR)		28 (58)	17 (20)	0,003
Gender	Male, n(%)	531 (%57)	56 (%45,5)	0,016
	Female, n(%)	400 (%43)	67 (%54,5)	
Araç	Ambulance, n(%)	494 (%53,1)	55 (%44,7)	0,082
	Self-admission, n(%)	437 (%46,9)	68 (%55,3)	
Season	Summer, n(%)	342 (%36,7)	32 (%26)	0,029
	Autumn, n(%)	181 (%19,4)	23 (%18,7)	
	Winter, n(%)	227 (%24,4)	44 (%35,8)	
	Spring, n(%)	181 (%19,4)	24 (%19,5)	
Cause	Work accident, n(%)	180 (%19,3)	0	<0,001
	Suicide, n(%)	88 (%9,5)	53 (%43,1)	
	Slipping/Fall/stumbling, n(%)	484 (%52)	47 (%38,2)	
	Falling from lap, n(%)	117 (%12,6)	23 (%18,7)	
	Other, n (%)	62 (%6,7)	0	
Pulse rate, Median (IQR)		77 (17)	106 (16)	<0,001
MAP, Median (IQR)		93 (12)	75 (27,7)	<0,001
GCS, Median (IQR)		15 (0)	8 (7)	<0,001
ISS, Median (IQR)		8 (11)	36 (24)	<0,001
Injured site	Head, n(%)	200 (%21,5)	95 (%77,2)	<0,001
	Neck, n(%)	132 (%14,2)	33 (%26,8)	<0,001
	Thorax, n(%)	140 (%15)	51 (%41,5)	<0,001
	Abdomen, n(%)	34 (%3,7)	25 (%20,3)	<0,001
	Ekstremiti, n(%)	601 (%64,6)	65 (%52,8)	0,011
	Spinal, n(%)	118 (%12,7)	84 (%68,3)	<0,001

IQR: İnterquantile range, MAP: mean arterial pressure, GKS: Glasgow coma score, ISS: Injury severity score, Other: Unknown reason.

## Discussion

In falls, in addition to the height of fall, many factors including age, cause of fall, type of floor fallen onto, injured body parts, and organ injury may determine patient prognosis. <sup>(6-8)</sup>

Erdem and Atay <sup>(12)</sup>, in a study on adults, reported that risk of fall increased as the age increased. İcer et al. <sup>(7)</sup> reported that, among patient's falling from a height, more than 70% of cases were children, and trauma severity and mortality rate were different in children than adults due to anatomic and physiological differences. In a study reported from India, the mortality rate was highest in women followed by children. <sup>(13)</sup> In our study, the patients falling from the same height had the lowest median age and those falling from a height less than 1 meter was highest. Furthermore, admitted and deceased patients were younger. This may be related to improper body balance in the toddlers and unawareness of objects and factors causing falls in the older children. The median age of patient falling from a height may have been 24 years due to patients working at height (construction worker, electrician, etc.) and those that committed suicide being young individuals. A greater trauma intensity in falls from a height and severe injuries resulting from uncontrolled falls among children may explain higher admission and mortality rates among young patients.

Nakada et al. <sup>(11)</sup> reported that 1 among all age groups males more frequently fall. Bulut et al. <sup>(14)</sup> reported that males had a higher proportion among children admitted for falls. Studies on the elderly have revealed that women fall more frequently. <sup>(15, 16)</sup> Erdem and Atay <sup>(12)</sup>, in an adult study, reported that the risk of fall increased among women. In our study 55.7% of our patient population was male, with the numbers of women who fell from the same height and who died were significantly higher. Minor trauma in female patients may cause death. Males engaging in aggressive games in childhood and more dangerous occupations sports in adulthood may explain why men fell more frequently.

Güzel et al. <sup>(17)</sup> studied pediatric patients and reported that falling height usually ranged between half a meter and one meter. İcer et al. <sup>(7)</sup> reported that falls usually occurred from heights less than 3 meters and falling height affected mortality rate. Dogan et al. <sup>(18)</sup> reported that 44.3% of traumatized children had simple falls and 16.4% fell from a height. We demonstrated that 13.1% of our patients fell from the same height; 37.2% from less than 1 meter; and 48.4% from more than 1 meter. We believe that children and older individuals fall from the same height or a lower height due to balance problems while younger

individuals fall from higher heights due to causes including suicide attempts and work accidents.

Pekdemir et al.<sup>(4)</sup> reported that 5.6% of trauma victims due to falls were transported to hospital by ambulance, and those patients were admitted at an increased rate. We showed that 52.1% of our patients were transported by an ambulance while those who fell from the same height more frequently presented to the emergency department with own means. We found no significant correlation between the type of admission and mortality and admission rates. We believe that the rate of ambulance transport has recently increased especially in severe trauma cases in line with recent advances in patient transport resulting in shorter patient access times. However, considering reaching the hospital earlier, families may have transported their children with less severe trauma with their own transport means. We believe that admission and mortality rates were unrelated to admission type since even simple trauma may lead to severe injuries in children and the elderly, some of who may present to the emergency department on an outpatient basis.

Güzel et al.<sup>(17)</sup> reported that falls most commonly occurred in summer among children. Akaoğlu et al.<sup>(5)</sup> reported that falls and sprains most commonly occurred in October and May. İçer et al.<sup>(7)</sup> reported that falls from a height usually occurred in summer. In a trauma series, the majority of which consisted of falls, Doğan et al.<sup>(18)</sup> reported that the frequency of admissions increased in the summertime. In our study falls most commonly occurred in summer months, and falls from a height particularly increased in summer and spring. Although the admission rate was higher in summer, the mortality rate was higher in winter. We believe that the revival of certain sectors such as construction in summer months and the tradition of sleeping on housetops increases the incidence of falls from a height in summer. On the other hand, mortality may be increased in winter since the victims of falls from the same height are usually children and older adults, who may succumb to even simple trauma episodes.

In a pediatric study, Güzel et al.<sup>(17)</sup> reported that the most common cause of fall was falling off the bed. Gören et al.<sup>(19)</sup> reported that 10.9% of total mortality secondary to falls occurring in suicide attempts and 89.1% due to accidental falls. In agreement with the literature reports, we most commonly observed accidental falls. Suicides and work accidents were associated with an increased rate for falls higher than 1 meter, admission, and mortality. We believe that accidental falls had a greater share due to our study enrolling pediatric subjects and domestic accidents as well as a lower awareness of icing

due to harsh weather conditions in winter. Suicidal falls and working accidents may have been associated with higher admission and mortality rates due to victims falling from a height and being exposed to multiple traumas.

Bruinjs et al. <sup>(20)</sup> reported that vital signs and ISS effectively predicted mortality; that blood pressure dropped, and ISS and pulse rate increased as trauma severity increased. Nakada et al. <sup>(11)</sup> reported that males had higher mortality; males had lower systolic blood pressure and GCS and a higher pulse rate and ISS. İçer et al. <sup>(7)</sup> reported that patients surviving falls from a height had a mean ISS of 8.76 and the deceased ones 24.72. İçer et al. <sup>(7)</sup> reported that the deceased patients had a lower GCS and a higher ISS. Evans et al. <sup>(15)</sup> reported that ISS ranged between 5 and 9 by the residence of the victim (house, nursery home, etc). Chippendale et al. <sup>(16)</sup> reported a mean ISS of 8.49 among the elderly with falls. Bulut et al. <sup>(14)</sup> reported that children admitted after fall had a mean ISS of 8.7 and a mean GCS of 13.3. In our study, patients falling from a height who were admitted and who were deceased had a higher pulse rate and ISS score whereas significantly lower GCS and MAP. We believe that as trauma severity worsened, vital parameters and scores worsened in parallel as a result of blood loss and impaired consciousness.

Güzel et al. <sup>(17)</sup>, in a study on children, reported that head trauma and soft tissue injury were the commonest injuries in falls. Bulut et al. <sup>(14)</sup> reported that, among children admitted for falls, head trauma was the commonest one followed by extremity injury. Evans et al. <sup>(15)</sup>, in a study on the elderly, reported that head injury developed at the highest rate. Nakada et al. <sup>(11)</sup> reported that head injury was the commonest in trauma patients. In a study on the elderly, it was reported that extremity injury and fracture rate increased. <sup>(16)</sup> Gören et al. <sup>(19)</sup> reported that among patients that died secondary to falls, head trauma was the most common injury followed by thoracic and abdominal trauma. Aufmkolk et al. <sup>(21)</sup> reported that multiorgan trauma and brain injury were the leading cause of death in patients falling from a height. We most commonly detected extremity and head injury. Injury rate in all localizations was higher among admitted and deceased patients. We believe that extremity injuries ranked top in falls from a height as a result of victims using their extremities to protect themselves during fall. Moreover, a higher incidence of femur fracture secondary to osteoporosis in the elderly patients may high and led to an increased rate of extremity injuries. On the other hand, uncontrolled falls may have brought head trauma to forefront in the pediatric age group. We believe that worsened trauma severity

increased the number of injured body sites, parallely increasing admission and mortality rates.

Chippendale et al. <sup>(16)</sup> reported an admission rate of 67.6% and a mortality rate of 4.6% among the elderly. Akaoglu et al. <sup>(5)</sup> reported that, among trauma patients of which 70% were due to falls, 10% of patients with local injury were admitted as were 37.8% of those with multiple traumas. Dogan et al. <sup>(18)</sup> reported that, among trauma patients of which 60.7% were due to falls, 33.5% were admitted to corresponding departments. İcer et al. <sup>(7)</sup> reported that, among cases of fall from a height, the mortality rate was 5.4%, and age, cause of trauma, fall height, vital signs, and trauma localization affected mortality rate. Bulut et al. <sup>(14)</sup> reported a mortality rate of 3.6% among children admitted for fall. Pekdemir et al. <sup>(4)</sup> reported that 8.7% of patients injured by a fall were admitted. In line with the literature data, our study revealed an admission rate of 24.2% and a mortality rate of 11.7%. Admission and mortality rates were related to age, gender, trauma severity, season, and vital parameters, as most studies suggested. We believe that every parameter affects mortality and admission rate, albeit to some degree.

Limitation of this study is that this research is a retrospective study and it is based on the patient's data.

### **Conclusion**

Falls may initiate an important process that may result in death. Patients of every age admitted after falls should be examined in detail and factors resulting in death should be excluded.

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# Chapter IX



# Clinical and Epidemiological Examination of Hyponatremia\*

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## Introduction

Hyponatremia, the most common electrolyte disorder in clinical practice, is defined as a serum sodium level lower than 135 mmol/L.<sup>(1, 2)</sup> It may develop as a result of a variety of mechanisms and may lead to diverse clinical manifestations ranging from mild symptoms to death.<sup>(3)</sup> Physiological alterations of the elderly, comorbidities, and medications make older people more susceptible to hyponatremia.<sup>(4)</sup>

Acute hyponatremia develops in less than 48 hours, usually as a result of excessive water intake or salt loss, and is more dangerous than chronic hyponatremia. Chronic hyponatremia, on the other hand, occurs due to more prolonged water retention and salt loss. Psychiatric patients, children, elderly with impaired cognitive abilities, and athletes constitute the majority of people deemed under risk.<sup>(5)</sup>

Sodium is the main determinant of serum osmolarity, and clinical signs are related to alterations in that parameter.<sup>(6)</sup> Hyponatremia can be classified as hypovolemic, hypervolemic, and euvolemic hyponatremia based on serum osmolarity.<sup>(7)</sup> Among hypovolemic causes of hyponatremia, there are acute corticosteroid withdrawal, cerebral salt loss, diuretic use, gastrointestinal losses, and iatrogenic causes (inadequate volume, use of hypotonic solutions); normovolemic causes include adrenal insufficiency, medications; hypervolemic causes involve acute renal failure, cirrhosis, and congestive heart failure.<sup>(7)</sup>

In the present study, we aimed to contribute to the existing literature by reviewing clinical and demographic properties of patients diagnosed with hyponatremia at the emergency department.

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\* This study was presented as an oral presentation on June 28-30, 2019 at the 2<sup>nd</sup> International Hippocrates Congress on Medical and Health Sciences, İstanbul, Turkey

## **Materials and Methods**

### *Patient population and study design*

The study was prepared according to ethical standards of the 1975 Helsinki Declaration's Human Experiment Committee which was revised in 2000. Our study was performed retrospectively among 239 patients who were admitted to the University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital Emergency Department due to any clinical condition and who were diagnosed to have hyponatremia between 1 January 2018 and 1 January 2019. Patients' medical data were accessed through patient cards and local data automation system.

Age, gender, comorbid conditions, medications, symptoms and signs, intensive care unit admission rates, and mortality rates were recorded and analyzed. Patients with a serum sodium level between 120 mmol/l and 135 mmol/l were included in group 1 and those with a serum sodium level below 120 mmol/l in group 2. Patients with missing medical information, age less than 65 years, and traumatic conditions were excluded.

### *Statistical analysis*

Data analysis was performed with SPSS (Statistical Package for the Social Sciences for Windows version 22.0 SPSS Inc., Chicago, IL, U.S.A.). The normality of data distribution was tested using the Kolmogorov-Smirnov test. Mann-Whitney U test was used to compare quantitative data and Pearson Chi-Square test to compare qualitative data. Quantitative data were expressed as mean and standard deviation (SD); qualitative data were reported as number (n) and percentage (%). A p value of less than 0.05 was considered statistically significant.

## **Results**

The study population had a mean age of  $69.71 \pm 4.32$  years, with those having mild hyponatremia having a significantly greater mean age ( $p < 0.05$ ). Fifty-six point one of the study subjects were female; the percentage of women was significantly greater among patients with severe hyponatremia ( $p < 0.05$ ). There was no correlation between smoking and hyponatremia ( $p < 0.05$ ). The most commonly used medications were furosemide and proton pump inhibitors. Among furosemide users, the rate of severe hyponatremia was greater ( $p < 0.05$ ). The comparison of the study groups in terms of the use of thiazides, spironolactone, calcium channel blockers, beta blockers, ACE inhibitors, proton pump inhibitors, antipsychotics, antiepileptics,

and antidepressants revealed no significant difference ( $p>0.05$ ) (Table 1).

**Table 1.** Comparison of demographic data of the patients

		Total	Group 1	Group 2	<i>p</i>
Age (year), Mean±SS		69,71±	70,68±	69,08±	0,00
Gender	Male, n(%)	105 (%43,9)	60 (%63,8)	45 (%31)	<0,0 01**
	Female, n(%)	134	34	100	
Comorbidity	Hypertension,	204	82	122	0,50
	Diabetes	167	68	99	0,50
	Malignancy,	27	10	17	0,79
	Cirrhosis, n(%)	24	8	16	0,52
	Dementia, n(%)	41	22	19	0,03
	Coronary artery	165	66	99	0,75
	Stroke, n(%)	33	12	21	0,70
Smoke, n(%)		166	66	100	0,83
Drug use	Furosemide,	121	30	91	<0,0
	Thiazide, n(%)	40	16	24	0,92
	Spironolactone,	50	20	30	0,91
	Calcium	49	21	28	0,57
	Beta blocker,	116	48	68	0,52
	ACE inhibitor,	105	48	57	0,07
	Proton pump	123	53	70	0,22
	Antipsychotic,	53	22	31	0,71
	Antiepileptic,	22	5	17	0,09
	Antidepressant,	55	21	34	0,84

\*Mann-Whitney U test, \*\*Pearson Chi-Square test, n: number of cases, SS: standard deviation,  $P<0.05$  was considered significant,

The inter-group comparison of vital signs also showed no significant differences ( $p>0.05$ ). Blood urea nitrogen (BUN) and creatinine (Cr) levels were above reference range although there was no significant inter-group difference with respect to creatinine of BUN levels ( $p>0.05$ ). Glasgow Coma Score (GCS) was significantly higher among those with severe hyponatremia compared to mild hyponatremia ( $p<0.05$ ). Confusion, sleepiness, nausea, epileptic seizures, and newly developed cardiac pathologies were significantly more common in those with severe hyponatremia ( $p<0.05$ ). The two groups had similar rates of headache, vomiting, and newly developed respiratory distress ( $p>0.05$ ). The intensive care unit admission rate was 20.9%, and it was significantly higher among those with severe

hyponatremia ( $p < 0.05$ ). The mortality rate was 4.6%, with the two groups having no significant difference ( $p > 0.05$ ) (Table 2).

**Table 2.** Comparison of clinical data of the patients

		Total	Group 1	Group 2	<i>p</i>
Diastolic blood pressure,		74,65±1	75±11,4	74,43±9	0,7
Pulse rate (bpm), Mean±SS		78,93±6	79±6,4	78,88±7	0,6
Blood urea nitrogen		63,07±1	64,06±1	62,42±1	0,5
Creatinine (mg/dl),		1,36±0,	1,36±0,	1,37±0,	0,9
GCS	14-15, n(%)	214 (%89,5)	91 (%96,8)	123(98 4,8)	0,0 11**
	13-8, n(%)	21	3	18	
	3-8, n(%)	4	0	4	
Signs and symptoms	Headache,	61	22	39	0,5
	Confusion,	17	2	15	0,0
	Nausea, n(%)	73	29	44	0,9
	Nausea, n(%)	63	18	45	0,0
	Sleepiness,	49	13	36	0,0
	Newly	8	0	8	0,0
	Newly	2	0	2	0,2
Epileptic	13	1	12	0,0	
Intensive care unit		50	10 (%)	40	0,0
Mortality, n(%)		11	5	6	0,6

\*Mann-Whitney U test, \*\*Pearson Chi-Square test, GCS: Glasgow Coma Score, n: number of cases, SS: standard deviation,  $P < 0.05$  was considered significant.

## Discussion

This study reviewed mild and severe hyponatremia cases with regard to age, gender, and etiological and clinical standpoints. Despite affecting all age groups, hyponatremia typically shows an increase in incidence with at advanced age groups.<sup>(5)</sup> This has been attributed to disturbed hormonal modulators of water and salt balance over time, renal insufficiency, increased prevalence of comorbidities, and medication use.<sup>(8)</sup> Former studies have shown that the mean age of hyponatremia cases is at a range of 71-76 years.<sup>(4, 9, 10)</sup> Our patients had a mean age of 69.7 years, with patients with severe hyponatremia being younger. We believe that hyponatremia incidence increases in the elderly due to physiological disturbances, increased frequency of comorbidities, and increased rate of medication use. Detection of mild hyponatremia in advanced age may stem from a greater frequency of hospital visits for follow-up and treatment. We believe that incidental

hyponatremia detected in routine blood samples taken at admission make asymptomatic cases clinically overt.

Prior studies have shown that women had a greater incidence of hyponatremia.<sup>5, 11, 12)</sup> This has been linked to estrogen, body fat ratio, and body water content in women.<sup>(5, 12)</sup> Nigro et al.<sup>(9)</sup> reported that 65% of hyponatremia cases were women while Falhammar et al.<sup>(10)</sup> 72%. We revealed that 56% of patients were women and severe hyponatremia was more common among women. This may have occurred since women's body mass index was lower and body fat/water ratio higher. Moreover, females were more commonly admitted to the emergency department due to infections, when they were incidentally detected with hyponatremia.

Former studies have reported that heart failure, advanced hepatic and renal disorders, inappropriate anti-diuretic hormone (ADH) release, and medications give rise to hyponatremia.<sup>(3, 5, 13)</sup> Particularly, congestive heart failure and hepatic cirrhosis have been shown to cause hyponatremia at a greater rate, related to ascites/water retention.<sup>(9, 14)</sup> Nigro et al.<sup>(9)</sup> reported that the most common comorbidities among patients with hyponatremia were hypertension and heart failure. Falhammar et al.<sup>(10)</sup> reported that hypertension was the most common comorbidity among patients with hyponatremia. Sweed<sup>(4)</sup> study reported that patients with hyponatremia had at least one condition affecting the nervous system. In the present study, the most common conditions were hypertension and coronary artery disease. While the incidence of mild hyponatremia increases in dementia, other comorbidities were unrelated to hyponatremia severity. We are of the opinion that low-salt diets, central nervous system disorders impairing ADH balance, and a plethora of medications used by patients with cardiovascular disorders led to an increased prevalence of hyponatremia. Additionally, it should be remembered that water retention due to conditions such as heart failure, cirrhosis may lead to hypervolemic hyponatremia. Especially inappropriate ADH syndrome and poor oral water and salt intake developing in dementia patients may have led to hyponatremia. As complaints of those patients cannot be clearly identified, they are frequently admitted to hospital and blood tests are ordered, which may have led to the detection of hyponatremia at an early stage.

It has been reported that most patients with hyponatremia chronically used medications and many medications were associated with hyponatremia, particularly thiazide diuretics.<sup>(3, 5, 13)</sup> Sweed<sup>(4)</sup> study reported that the frequency of diuretic use was greater in patients with hyponatremia compared to individuals of similar age, and the

frequency of use of other drugs was similar with that of the control group.

Many psychiatric medications and antiepileptics have been implicated in hyponatremia.<sup>(2, 15-17)</sup> Additionally, excessive water intake by psychiatric patients has been reported to increase hyponatremia prevalence to 20–47%.<sup>(13, 18)</sup> Falhammar et al.<sup>(10)</sup> reported that patients with hyponatremia had a higher rate of proton pump usage, with current use of proton pump inhibitors creating no risk for hyponatremia but newly administered ones posing a threat. Hyponatremia in that condition was attributed to inappropriate ADH syndrome and interstitial nephritis. In our study the patients most commonly used furosemide, proton pump inhibitor, and beta blockers. Patients using furosemide were most likely to have severe hyponatremia. Other medications were not related to hyponatremia severity. Many medications, mainly those used to force diuresis, impair water and electrolyte balance. On the other hand, disorders for which medications were administered could also lead to hyponatremia. We believe that widescale use of furosemide to relieve edema as well as salt restriction, additional disorders complicating the clinical situation leading to poor oral intake and contributing hyponatremia development.

Eckart et al.<sup>(19)</sup> reported that hyponatremic patients were more likely to be hypotensive and tachycardiac than the control group. However, the means of the vital parameters were within reference ranges Nigro et al.<sup>(9)</sup> also found that vital parameters were within the reference range. In our study, there was no correlation between hyponatremia severity and vital parameters.

This may be related to the fact that alterations of vital parameters may be related to serum osmolarity rather than hyponatremia. We believe that vital signs remained unchanged as we had hypo-, hyper-, and euvolemic patients in our study population.

Verbrugge et al.<sup>(20)</sup> reported that the BUN/Cr ratio increased in hyponatremia cases, which was associated with plasma renin activity and aldosterone level. It is well known that a higher BUN/Cr ratio mostly indicates dehydration and lower ratio overhydration.<sup>(2)</sup> Sweed<sup>(4)</sup> study revealed that BUN and Cr levels were higher in hyponatremic patients than the controls. Although BUN and Cr levels were above reference ranges in hyponatremic patients of our study, the study groups showed no significant difference. We believe that in those patients hyponatremia basically developed secondary to hypovolemic hyponatremia which increased BUN and Cr levels. However, identification of patients at an early stage and the higher

prevalences of other causes of hyponatremia may have obscured the statistical significance between BUN and Cr levels.

It has been reported by multiple studies that hyponatremia may have a clinical spectrum from asymptomatic disease to nausea, numbness, convulsions, and coma.<sup>(6, 9, 21)</sup> Clinical signs of hyponatremia are related to brain edema development and proportional to sodium level and the rate of hyponatremia development.<sup>(6, 9, 21)</sup> Symptoms usually start 24 hours earlier than hospital admission.<sup>(5)</sup> In that study, impaired consciousness was present in 77% of patients and seizures in 67%.<sup>(5)</sup> Nigro et al.<sup>(9)</sup> reported that the most common symptoms among hyponatremic patients were nausea (44%) and vomiting (30%), with rare complications of epileptic seizures having a rate of around 5%. In our study the patients most commonly complained of nausea and vomiting followed by headache; those with severe hyponatremia had a lower GCS and higher rates of confusion, vomiting, epileptic seizure, and newly developed cardiac pathology. We are of the opinion that as hyponatremia severity worsens, the frequency of brain edema increases with the parallel intensification of symptoms. We also believe that that electrolyte disorder causes cardiac conduction and mechanic disturbances.

Patients with hyponatremia need to be hospitalized for correction of serum sodium level and identification and treatment of the underlying cause. However, it has been reported that patient with acute hyponatremia needs intensive care and dies more frequently.<sup>(9)</sup> Hyponatremia is usually associated with neurological signs and increased mortality.<sup>(5)</sup> Eckart et al.<sup>(19)</sup> reported that hyponatremia and vasopressin activation were among factors increasing mortality. Furthermore, chronic hyponatremia is implicated for increased morbidity and mortality.<sup>(21, 22)</sup> Nigro et al.<sup>(9)</sup> reported an intensive care unit admission rate of 35% and a mortality rate of 4% among patients with hyponatremia. In our study, 20.9% of our patients needed intensive care and 4.6% died. Severe hyponatremia was associated with a significant increase in the need for intensive care but there was no correlation between mortality and hyponatremia severity. We believe that an increased rate of impaired consciousness due to brain edema with severe hyponatremia increased the need for intensive care. We believe the groups were not significantly different with respect to mortality rate due to a low mortality rate and hyponatremia being accompanied by other conditions (sepsis, poor oral intake, etc.).

The main limitation of our study is its retrospective nature, which precluded patient follow-up. Moreover, duration of use and dose of medications were not taken into consideration, which prevented us

from making an analysis of whether there was a possible relationship between duration of use and dose of medications and hyponatremia.

### **Conclusion**

Hyponatremia is an electrolyte disorder that may develop due to a variety of causes and lead to diverse clinical signs and symptoms. One should be watchful about possible mortality development was especially among elderly patients with hyponatremia.

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# Chapter X



# Free Flap Reconstruction of Upper Extremity

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Burns, tumor resections, infections and trauma are the main etiologies of upper extremity soft tissue defects. Skin grafts, local-regional flaps and free flaps can be used in the reconstruction of upper extremity defects.[1] The upper extremity anatomy serves many local flap options for the reconstruction of small defects. Although local and regional flaps have better color and tissue adaptation, they create additional morbidity to the injured extremity. Lack of appropriate texture and composition are other limitations. For the reconstruction of large and complex defects, free flaps are essential.

Preoperative planning should be considered after a good wound debridement.

Highlights in preoperative planning:

- a. Mechanism of injury
- b. Location and size of the defect
- c. Exposed structures
- d. Status of surrounding tissues, presence of vascular injury
- e. Presence of infection/ contamination
- f. Whether or not sensory reconstruction is needed
- g. Potential donor sites [2]

Reconstruction time after injury is controversial. [3] Ninkovic classified the reconstruction time as "primary free flap closure" (12 to 24 hours), "delayed primary free flap closure" (2 to 7 days), and "secondary free flap closure" (after 7 days).[4] It is stated that reconstruction in the first 24 hours reduces infection and increases flap viability.[5] Today, many surgeons believe that reconstructions at "the earliest possible time" reduces hospital stay, reduces infection and fibrosis, and enables early mobilization of the extremity. Also it is cost effective.[6]

Flaps frequently used by the author in upper extremity reconstruction:

Radial forearm flap

Anterolateral thigh flap

Lateral arm flap

Latissimus dorsi muscle flap

Fibula osteocutaneous flap

### **Radial Forearm Flap**

The first clinical studies were published in Chinese in 1980. For this reason, it is also called “Chinese flap. It was introduced to the western world by German surgeons who visited China in 1980. The first articles about the flap are its use as a free flap. [7]

Its pedicle is the radial artery. Pedicle length can be up to 20 cm. Mean artery diameter is 3 mm and concomitant veins are 1-2 mm in diameter. Diameter match with the upper extremity is excellent. Cephalic vein can also be included in the flap for extra venous drainage in large flaps.

Before the flap is planned, the Allen test must be performed to ensure that the extremity is well perfused by the ulnar artery.

The flap is elevated with the septum between the brachio radial and the flexor carpi radialis, preserving the paratenons of the flexor tendons. The entire forearm can be obtained as a flap. But 5 cm of dorsal skin should be left intact over extensor tendons. The antebrakial cutaneous nerve can be harvested in the flap for a sensory flap. The flap donor site is reconstructed with partial thickness skin graft. The most important disadvantage is donor site morbidity.

#### ***Advantages:***

- It is thin.
- It can be harvested with bone and tendons.
- Suitable for sensory reconstruction.
- Surgical technique is simple.
- The vascular diameter match with the upper extremity is excellent.
- Pedicle is long.
- It is suitable for use in large defects.

#### **Case**

28 year olded male, work related crush injury. Debridment and revascularization performed. Palmar, dorsal and 5th finger necrosis observed during follow-up. Debridment and reconstruction with free radial forearm flap performed at post operative 2nd week. Early post-op and 1 year post-op photos below.



### Donor Site

Intraoperative and postoperative 1 year. No functional deficit at donor extremity.





### **Anterolateral Thigh Flap**

In 1984, it was described by Song et al. Pedicle: descendent branch of the lateral circumflex femoral artery. And this is elevated with its septocutaneous and musculocutaneous perforators. The pedicle length is approximately 12 cm. The arterial and venous diameters are approximately 2 mm. Flap can be harvested together with the Vastus lateralis muscle when bulk is needed. Suitable for reconstruction of large defects. (20x25 cm) Flap can be quite thick in patients with high BMI. Suprafascial dissection should be performed when thin flap needed.

A line is drawn from the anterior superior iliac spine to the superolateral edge of the patella. The midpoint of this line is marked. A 2 cm circle is drawn. Perforators feeding the skin are often found in the lower distal part of the circle. After determining the perforator by hand doppler or other imaging methods, the flap is elevated according to the perforator flap concept.

#### ***Advantages:***

- It can be used for reconstruction of large defects.
- Vastus lateralis, rectus femoris and tensor fascia lata can be used together as chimeric flap.
- Tensor fascia lata tendon graft can be taken from the same area.
- Vascular diameter match with the upper extremity is good.

- It can be harvested with lateral femoral cutaneous nerve branches for sensory reconstruction.

**Case**

18 years old, male patient, work related injury with vascular injury. Debridment, vascular repairs with vein grafts performed. Suprafascial anterolateral thigh flap used for soft tissue reconstruction.



Photo of injured hand in emergency department.

Flap markings, harvested suprafascial ALT flap, early post-op and late postop photos of hand and donor site respectively.





### **Lateral Arm Flap**

It is a septofasciocutaneous flap defined in the early 1980s. The pedicle is the posterior branch of radial collateral artery. The average pedicle length is 6 cm. Vascular diameter of pedicle vessels are 1.5 mm. It is often drained with 2, sometimes single concomitant veins. It has a reliable fixed anatomy. It is suitable for use in many different regions. Donor site morbidity is low. The lower brachial cutaneous nerve can be harvested of sensory flap.

The line drawn from the deltoid insertion to the lateral epicondyle shows the posterior septum. Posterior septum is located between the triceps muscle and the brachialis / brachioradialis. The flap is

harvested with this septum, including the periosteum. When the proximal flap dissection is reached, attention should be taken to the radial nerve. When the pedicle dissection is complete, the flap's artery and vein should be marked with stiches. If not, the artery and vein can be confused.

***Advantages:***

- It is thin.
- Donor site morbidity is low.
- Suitable for sensory reconstruction.
- The distal posterolateral of the humerus can be harvested with the flap. (Osteofasciocutan flap) The author does not use this flap as an osteofasciocutane because of the risk of humeral fracture.

**Case**

78 year olded man, suffered from diabetic hand infection. Debridment and reconstruction with lateral arm flap performed.



## Latissimus Dorsi Muscle Flap

It was first used by Tansini in 1906 as a pedicle for reconstruction of large mastectomy defects. [8] Today, it is widely used as pedicled and free flap. The pedicle is the thoracodorsal artery. The pedicle length is approximately 8 cm. The mean vascular diameter is 3 mm. The most important advantage is that it can be used in reconstruction of large defects. It can be used together with the skin island or just as a muscle.

### *Advantages:*

- Suitable for reconstruction of large defects.
- Fast, easy and safe dissection.
- Suitable for vertical, horizontal and oblique skin island planning.
- If it is desired to reconstruct large areas with a thinner flap, it can only be transferred with the muscle component.
- Suitable for functional transfers.
- It can be planned as a chimeric flap with scapular and parascapular system.

### **Case**

24 years olded male, work related injury. Vascular structeres are exposed, almost total sircular defect at the elbow. Reconstructed with latissimus dorsi muscle flap. End to side anastomosis performed to brachial artery and end to end anastomosis to the superficial veins.



## Fibula Flap

Nowadays, due to high energy upper extremity injuries (traffic accidents-explosions), upper extremity complex defects occur.

Reconstruction with bone graft can cause fracture healing problems. For this reason, composite reconstructions with vascularized bones are essential. Vascularized bones provide optimal results with physiological healing patterns.

Vascularized fibula transfer was described by Taylor in 1975.[9] It has revolutionized reconstructive surgery. It is currently the first choice for reconstruction of mandible and long bone defects.

Its pedicle is peroneal artery. The vascular diameter is 2.5 mm. In adults, high-density cortical bone can be provided up to 25 cm.[10] The head of the fibula and lateral malleolus are marked. A minimum of 6 cm in the superior and 4 cm in the inferior segment of bone are not removed for stability of the knee and ankle joints. Skin perforators are found with the Doppler probe and the skin island is marked. The flap is located in the center of the posterior septum.

***Advantages:***

- Compared to other vascularized bone donor sites in the body, it is very suitable for limb reconstruction because it provides a long and straight bone.
- The compatibility of the fibula with the diameters of the radius and ulna is very important for forearm reconstructions.
- It is also advantageous for the reconstruction of large bones such as humerus, tibia, femur to the medullary cavity.

**Case**

48 years old male, gunshot injury with ulnar lateral soft tissue and 9 cm ulna bone defect reconstructed with free fibula osteofasciocutaneous flap.



### Conclusions

In a successful upper extremity reconstruction, it is very important to provide a stable skin cover and functional reconstruction. Prolonged immobilization may impair hand and finger functions. Therefore, reconstruction of the upper extremity defects should be performed as early as possible. The free flaps provides this requirement very well. It is a developing area with many free flap options for upper extremity reconstruction. The aim of this book chapter is to briefly introduce the free flaps that we use most frequently in the upper extremity reconstruction. It is recommended that those who wish to develop themselves in this complex area should attach importance to additional readings and training.

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## **Chapter XI**

# Cutaneous Meningiomas: A Systematic Review and Meta-Analysis of Case Reports

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## Introduction

Meningioma is a tumor originating from meningeothelial cells of meninges in the central nervous system.<sup>1,2,8</sup> It is the most common tumor of neuroaxis and is also the most common (15-30%) extracerebral intracranial tumor.<sup>1-8</sup> They are mostly seen in the seventh decade.<sup>3</sup> They are rarely seen in childhood but they are more aggressive.<sup>1,4</sup> Since these tumors originate from the meninges, they show a classic meningeal location.<sup>9</sup> Most of them, therefore, surround the brain or ventricles.<sup>9</sup> Some may be locally invasive and most are benign although malignant ones have been reported.<sup>3</sup> They grow slowly over the years.<sup>2,3</sup>

Cutaneous meningioma is a tumor originating from ectopic meningeothelial cells in the dermis and subcutaneous tissue outside the central nervous system.<sup>1,2,8,10</sup> They are rare cases.<sup>8</sup> Cutaneous meningiomas account for less than 2% of meningiomas.<sup>6,11-14</sup> They are most commonly occur on the scalp.<sup>2,14,16</sup> They may occur both congenital and acquired.<sup>17</sup> Cutaneous meningiomas are composed of various lesions with different pathogenesis and prognosis.<sup>1</sup> There is a wide range of clinical differential diagnoses, but the diagnosis is made by characteristic histological and cytological findings. Congenital tumors often occur after birth and even in adulthood.<sup>11</sup> Acquired tumors are seen in adults.

Cutaneous meningioma (Psammoma) was first reported by Max Winkler in 1904.<sup>8,18,19</sup> The largest and most cited report by Lopez et al. in 1974 provided the basis for the classification system of cutaneous meningiomas. However, most of the literature on these tumors is case reports reflecting their rarity. Lopez et al. studied 25 cases of cutaneous meningiomas that presented as skin and/or subcutaneous tumors. They divided these cases into three groups based on different etiologies on the basis of clinical and histological features: Type I-

Primary (Congenital) cutaneous meningioma, Type II-Ectopic meningioma of soft tissue spreading to the skin, and Type III-Secondary, spreading to skin from intracranial meningioma.

Type I cutaneous meningiomas are congenital.<sup>1,8,11,20-22</sup> They usually occur on the occipital region of the scalp or along the suture lines and in the paravertebral region.<sup>1,2,8,22-24</sup> They are caused by ectopic meningotheelial cells entering into the dermis or subcutis during embryonic or fetal development.<sup>1,8,9,11,15,25</sup> This is due to the fact that all nerve elements cannot be completely confined to the neurotropic nerve tissue during the closure of the neural tube.<sup>1,9</sup> The rudimentary meningoceles and acoelic meningeal hamartomas caused by this mechanism most probably represent the ends of a spectrum.<sup>9</sup> Many authors prefer the term cutaneous meningioma for these entities.<sup>9</sup> The fact that some type I cutaneous meningiomas have a connection with the central nervous system such as sinus tract suggests that type I cutaneous meningiomas may be rudimentary meningoceles that have no connection with the central nervous system.<sup>1,8,9</sup> Type I cutaneous meningiomas have many common features with meningoceles, and the occurrence of both is likely to be similar.<sup>1,9,26</sup> Similarly, meningocele has been suggested to be caused by the "compression" of the meningeal tissue to the surface due to the delayed closure of the neural tube resulting in the herniation of the meninges, or possibly early closure of the neural tube.<sup>1</sup> A similar phenomenon may occur in both types of congenital lesions. The difference is that the tumor represents hyperplasia of the arachnoid cell and is associated with fibrocollagen proliferation and obliteration of the cystic cavity.<sup>1</sup> It is essential that these tumors do not have intracranial or intravertebral neuraxis meningioma.<sup>1</sup>

Type II cutaneous meningiomas are acquired.<sup>1,8</sup> They occur as a result of the spread of soft-tissue meningiomas arising from cell remnants of ectopic meningiomas found along the cranial and spinal nerves close to the skin into the skin and/or subcutaneous tissue.<sup>1,8</sup> Therefore, they usually occur around the sensory organs (eye, ear, nose, and mouth) and along the traces of the cranial and spinal nerves.<sup>1,8</sup> As with type I cutaneous meningiomas, it is essential that the patient does not have a neuraxis meningioma.<sup>1,8</sup> Tumors are extracranial or extravertebral. They are typically seen in adults but can occur at any age.

Type III cutaneous meningiomas are caused by the direct progression of a neuroaxis meningioma (primary intracranial meningioma in general) to the skin or subcutaneous tissue along the bone defects and defects after surgery or trauma, herniation of a neuroaxis meningioma, implantation during a surgical operation, or

direct skin or subcutaneous metastasis by destructing the bone through direct invasion.<sup>1,8</sup> Therefore, these tumors are much more common in adults.<sup>8</sup> They are mostly seen in the face and scalp.<sup>8</sup> The general condition of patients is often poor.

### **Clinical findings**

Type I cutaneous meningiomas are seen as firm subcutaneous nodules and they may, sometimes, be polypoid or even pedunculated.<sup>1,11,22,27,28</sup> One case was elastically soft.<sup>29</sup> Hair tufts, hypertrichosis areas, alopecia areas, aplasia cutis congenita, dermal melanocytosis and pigmentation can be seen on the skin above or around it, or it may be covered with normal skin.<sup>6,11,20,21,29-36</sup> Although it is usually painless, some patients may have pain or tenderness.<sup>37</sup> They are usually asymptomatic.<sup>1,17,20</sup> Neurofibromas may coexist with acoustic neuroma.<sup>38</sup> First-degree relatives may have Von Recklinghausen disease and neurofibromas, meningiomas, and gliomas.<sup>38,39</sup> Fluctuations were reported in a case report. They could be familial. Dermal sinus associated with the dura mater may be present, or there may be an intradural connection with the phylum terminal, or bone defects.<sup>11,22,35,40</sup>

Type II cutaneous meningiomas are also seen as firm subcutaneous nodules. They are painless in general but sometimes painful.<sup>41</sup> They are asymptomatic at the beginning, but they often become symptomatic over time due to their proximity to the sensory organ, cranial or vertebral nerve.<sup>1</sup> The following symptoms may occur: ipsilateral or bilateral proptosis, periorbital edema, hardening of the eyelids, lateralization, hearing loss, chronic rhinitis or sinusitis, nasal polyp, glossoplegia or atrophy of the tongue, facial nerve palsy, paresis or paralysis of the extremities, or secondary epilepsy.<sup>1,2,42</sup> Type II tumors around the sensory organs can be clinically confused with granulation tissue and inflammatory processes at first.<sup>1,8</sup> They may be associated with skull fractures.<sup>2,5,10,43,44</sup> Encephalomalacia due to fractures may occur.<sup>2,5,43</sup> There were two cases associated with low dose radiotherapy.<sup>15,45</sup> One case was excised with an acceleration of tumor growth in the third trimester of pregnancy.<sup>46</sup> One case was a 14-years old boy with malignant meningioma.<sup>47</sup> Two years later, lung and pleural metastasis were detected. In this case, PanCK positivity was remarkable.<sup>47</sup>

Type III cutaneous meningiomas are also seen as round, firm subcutaneous nodules. They were usually immobile.<sup>7,48-50</sup> Masses can be painful, tender, hemorrhagic and ulcerated.<sup>7,48,51</sup> Complete obliteration of superior sagittal sinus by tumor, tonic and clonic seizures, headache, nausea, visual disturbances, speech disinhibition,

paraparesis or paraplegia can be seen.<sup>7,48,52-54</sup> There may be a history of intracranial meningioma resection.<sup>7,48,55</sup> World Health Organization (WHO) grade I intracranial meningioma may eventually become WHO grade II or III intracranial meningioma.<sup>48</sup> Cerebrospinal fluid fistula or meningitis may develop as a complication. Neurological examination may also be normal.<sup>50</sup> The duration of the occurrence of lesions may vary from a few weeks to a few years.<sup>7,56</sup> They generally have a poor prognosis.<sup>1,41,48</sup> A 12 year-old case was reported exceptionally in a study.<sup>57</sup> Two patient had metastasis to the cervical lymph nodes. Most of the cutaneous meningiomas were localized in the scalp, face and paravertebral region.<sup>12,16,58</sup> One case was in the middle phalanx of the 5th finger of the right hand.<sup>7,12,59</sup>

### **Macroscopic findings**

Tumors appear as solitary or multiple, hard, gray/white, and yellow subcutaneous nodules in sizes ranging from a few millimeters to 20 centimeters.<sup>6,7,13,60</sup> In type I cutaneous meningiomas, clear fluid discharge or disproportionate bleeding may occur during the excision of the tumor in proportion to the size of the lesion if the tumor has a deep connection.<sup>1</sup> Depending on the depth of the tumor, there may be underlying soft tissue, fascia or bone involvement.<sup>10</sup> They may have cystic cavities.<sup>61</sup> Some tumors may develop close to the nerves. Type II or III tumors can erode the underlying bone.<sup>7</sup> Type I tumors generally had a whitish fibrous solid cross-sectional surface.<sup>1</sup> In acquired tumors (Type II and III), the samples were generally more superficial and consisted of gray tissue fragments.<sup>1,8</sup> Type III cutaneous meningiomas may be ulcerated and be adhered to the brain parenchyma.<sup>7,48</sup> The largest tumor ever reported weighed approximately 3.4 kg.<sup>48</sup>

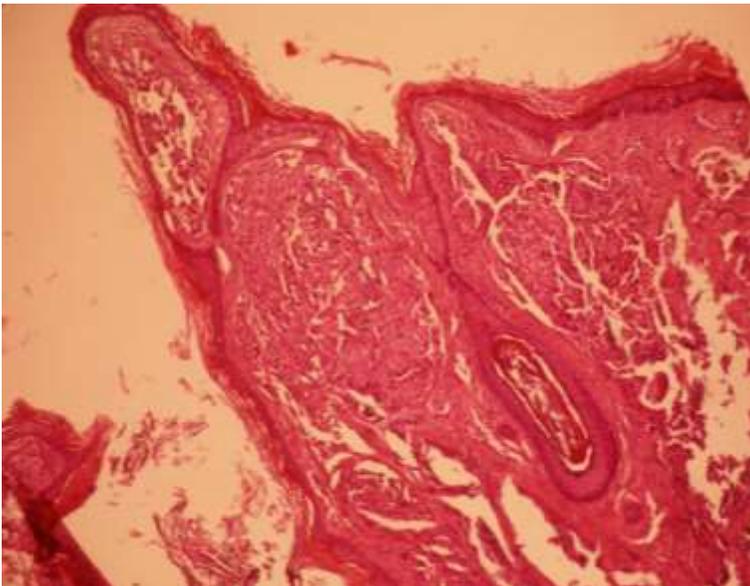
### **Microscopic Findings**

There was tumor with a poorly-defined border usually in a syncytial growth pattern, which consisted of nests of spindle and meningothelial cells and had whorl-like structures, accompanied by psammoma bodies and collagen bodies (Figure 1, 2 and 3).<sup>1,8,12,17,19,20,25,28,29,62-65</sup> Rare intranuclear inclusions were present.<sup>1,12,17,62</sup> There was no epidermal involvement. Lesions called type I variants or acoelic meningeal hamartomas were usually composed of scattered foci of hyperplastic meningothelial cells and psammoma bodies in subcutaneous tissue. Type I cutaneous meningiomas, also called rudimentary meningoceles, were neoplastic stalk lesions consisting of the rudimentary cystic cavity and nests or cords of meningothelial cells.<sup>11,22</sup> Necrosis, cellular atypia, and mitotic activity were absent or low in general (Figure 2) and the Ki-67 index

was also low.<sup>8,17</sup> Meningothelial cells had oval or round basophilic nuclei with uniform, dispersed, fine chromatin, and pale eosinophilic cytoplasm (Figure 2).<sup>1,2,29</sup> Cytoplasmic borders were unclear (Figure 2).<sup>1,29</sup> In type I cutaneous meningiomas, there were only mast cells as additional cells.<sup>1</sup> In one case, eosinophils were also accompanied.

Acquired lesions (Type II and III) had similar cytological features to congenital tumors, but they generally contained less collagen and were more lobulated and cellular.<sup>1</sup> Typically, there were more collagen bodies than type I lesions.<sup>1</sup> Acquired tumors were accompanied by a variable number of inflammatory cells including polymorphonuclear leukocytes, eosinophils, and lymphocytes.<sup>1,61</sup> As in type I tumors, a variable number of psammoma bodies were present in the acquired tumors. However, collagen bodies were typically more prominent than type I tumors.<sup>1</sup>

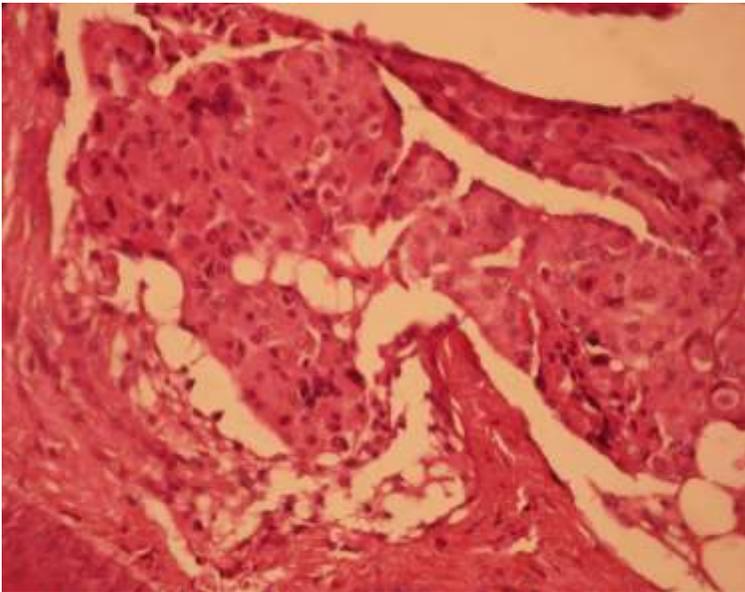
Mild pleomorphism and infiltrative growth pattern may be seen in type II tumors.<sup>1</sup> This may infiltrate the surrounding tissue and muscle tissue.<sup>1</sup> Ki-67 proliferation index and mitotic activity may be slightly high.<sup>61</sup> Epithelial cell layers, thin-walled vessels, and small lymphocytic aggregates may be observed in syncytial growth pattern. Hyperchromatic nucleus, uneven nuclear membranes and rare intranuclear pseudoinclusions may occur. Solid layers and psammoma bodies of meningothelial cells can be seen in dense collagen tissue.<sup>41</sup>



**Figure 1:** In a type II meningioma located in the external auditory canal, skin consisting of cell nests and subcutaneous polypoid tumoral

proliferation were seen in fibrous stroma covered with squamous epithelium. (H&E, 10x)

There might be necrosis areas in type III tumors. Pleomorphism is usually seen in atypical tumors, but may not be present in some tumors. Mitosis rate is usually slightly high or high. Extracranial mass usually shows histopathological features similar to intracranial mass. Intracranial tumors may be WHO Grade II or III (atypical or anaplastic) meningioma.<sup>66</sup> They can be rarely WHO Grade I which may present with multiple recurrences in craniotomy sites.<sup>67</sup> Atypical meningiomas (WHO Grade II) may also metastasize. Brain invasion is seen in general.<sup>7,48</sup> One case had a secretory malignant meningioma that resembled slightly differentiated carcinoma. There were plenty of secretory granules.



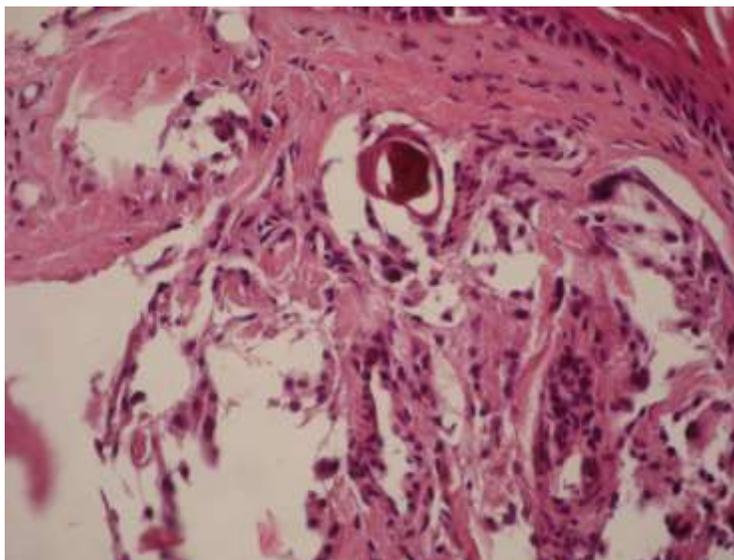
**Figure 2:** In cutaneous meningioma, tumoral proliferation consists of large cell nests in a syncytial growth pattern of large polygonal or round cells, which had hypochromatic oval or round large nucleus without nucleolus and had uncertain cell borders with eosinophilic cytoplasm. No significant mitotic activity and cytological atypia were observed in proliferating neoplastic cells. (H&E, 40x)

### **Differential Diagnosis**

Clinical and histopathological differential diagnosis was extensive. The clinical and histopathological differential diagnosis generally included nevus sebaceous, epidermal and trichilemmal cyst, melanocytic nevi, adnexal tumors, sebaceous cysts, skin tag, seborrheic keratoses, chalasion, dermoid cyst, lymphangioma, fibroma,

neurofibroma, osteoma, glioma, hemangioma, lipoma, scar, verrucous hamartoma, alopecia areata, squamous cell carcinoma, malign proliferating trichilemmal tumor, hemangioma, giant cell fibroblastoma, hidradenoma, hidradenocarcinoma, hemangiopericytoma glomus tumor, granular cell tumor, xanthoma, carcinoid tumor, and clear cell carcinoma metastasis, melanoma, paraganglioma, schwannoma, olfactory neuroblastoma.<sup>1,8,19,32,61,68,69</sup>

Most of the epithelial tumors can be easily histopathologically differentiated by the presence of keratinization, follicular, sebaceous or sweat gland differentiation, and neuroglial lesions.

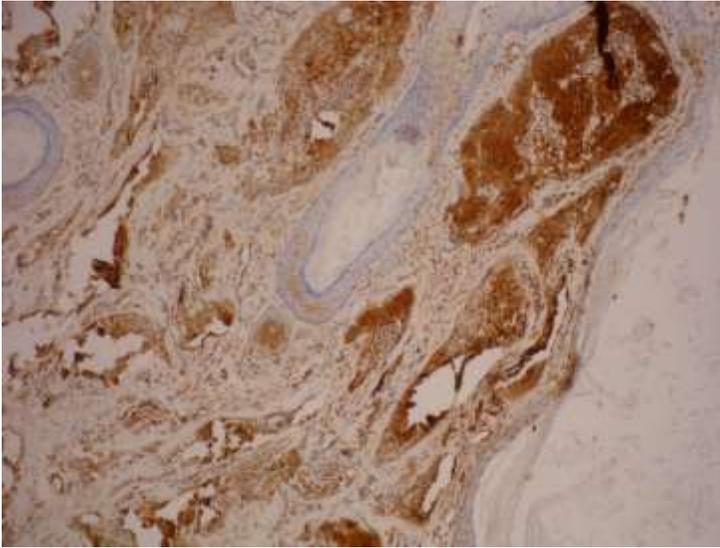


**Figure 3:** Cutaneous meningioma contains a psammoma body in the nest (H&E, 40x)

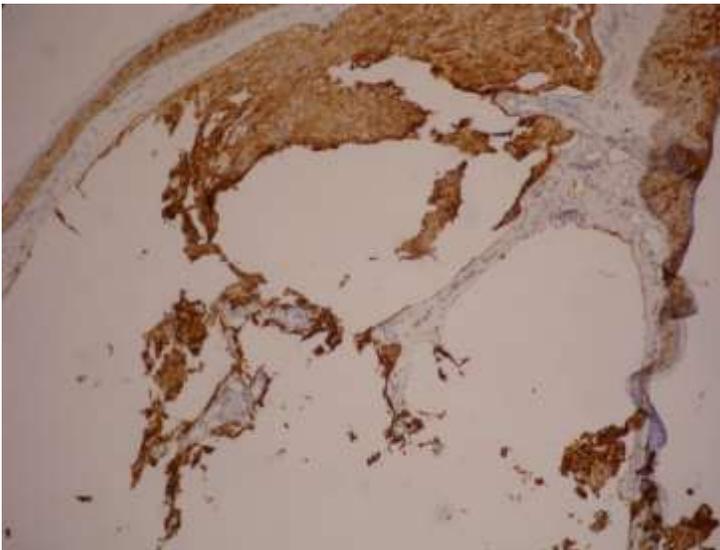
### **Immunohistochemistry**

Differential diagnosis can be confirmed by the use of immunohistochemical stains in the diagnosis of cutaneous meningiomas that cannot be histopathologically identified. Epithelial membrane antigen (EMA), progesterone receptor (PR) and vimentin positivity support the diagnosis of meningioma (Figure 4, 5 and 6).<sup>2,8,11,41,64,70-72</sup> Furthermore, cytokeratins can be used to exclude epithelial lesions (Figure 7); S-100 protein, melan-A, and HMB-45 can be used to exclude melanocytic lesions (Figure 8); CD31 and CD34 can be used to exclude vascular endothelial tumors; CD68 and CD163 can be used to exclude histiocytic tumors; SMA and desmin can be used to exclude myogenic tumors.<sup>2,8,71</sup> One case was stained with NF and seven cases with S-100 protein.<sup>17,24,63,71,73</sup> Four cases

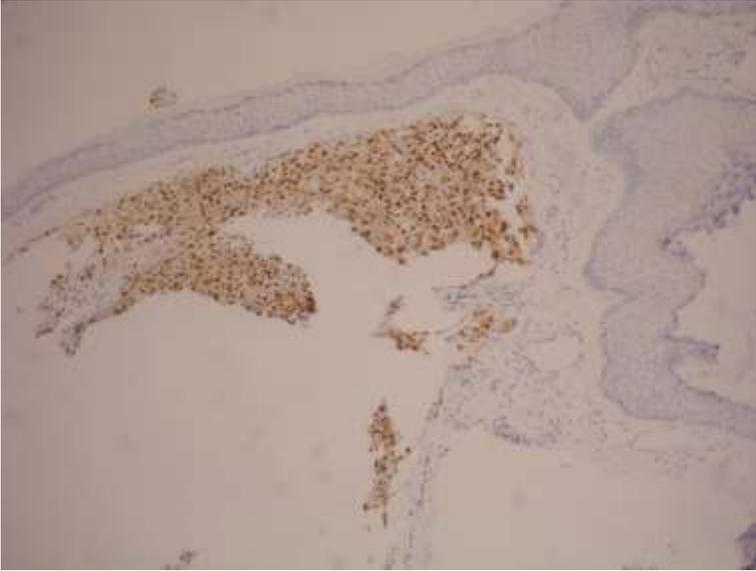
were not stained with EMA.<sup>29,74</sup> One case was stained with PanCK. One case was in part stained with desmin.<sup>29</sup>



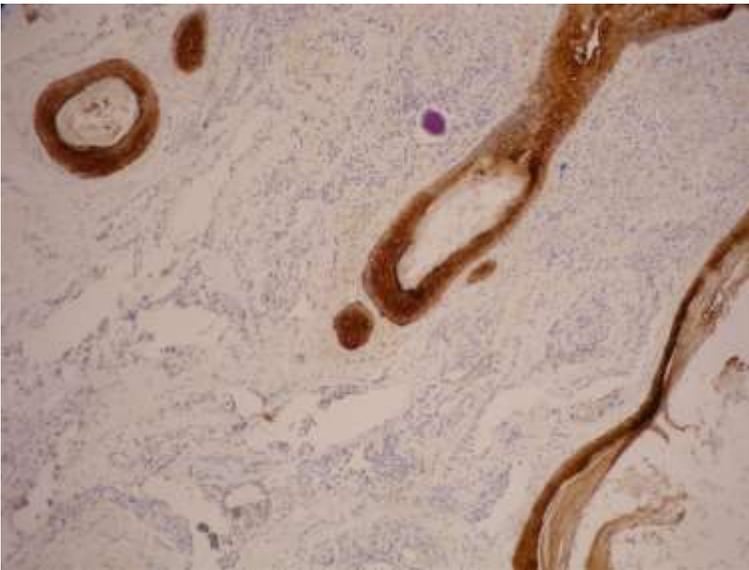
**Figure 4:** Immunohistochemical examination of cutaneous meningioma shows that neoplastic cells are stained with vimentin. (Vimentin, 10x)



**Figure 5:** Immunohistochemical examination of cutaneous meningioma shows that neoplastic cells are stained with EMA. (EMA, 40x)

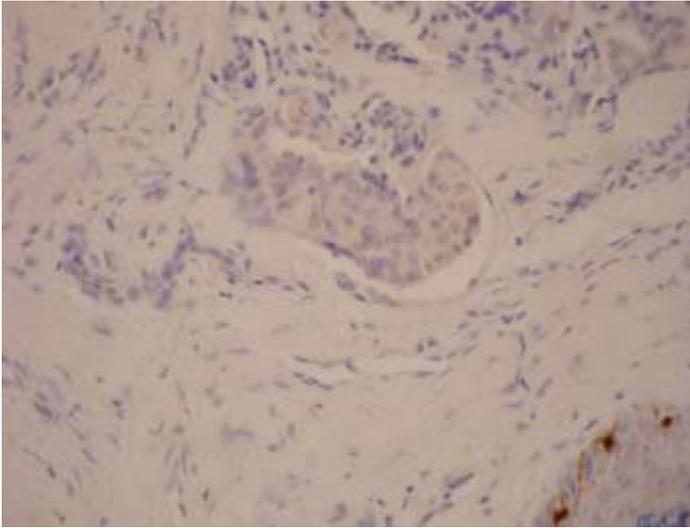


**Figure 6:** Immunohistochemical examination of cutaneous meningioma shows that neoplastic cells are stained with PR. (PR, 40x)



**Figure 7:** Immunohistochemical examination of cutaneous meningioma shows that neoplastic cells are not stained with

cytokeratin AE1/AE3 while surface epithelium is stained. (Cytokeratin AE1/AE3, 40x)



**Figure 8:** Immunohistochemical examination of cutaneous meningioma shows that neoplastic cells are not stained with S-100 while melanocytes in the basal layer of the squamous epithelium are stained. (S-100, 40x)

### **Treatment**

The basis of treatment is complete surgical excision.<sup>8</sup> Prognosis depends on the type of lesion. Type I lesions have a very good prognosis. No recurrence has been reported in these tumors. On the other hand, type II and III lesions have a worse prognosis. Surgical intervention may not be suitable for type III lesions located in surgically problematic areas. In such cases, the tumor-related prognosis depends on the amount of tumor remaining, the growth rate of the tumor, and degree of compression of the tumor in vital organs. Radiological examination should be performed before surgical treatment in order to determine the prevalence of neoplasm and surgical operation should be planned accordingly. This helps to minimize errors and complications. The aim of surgical treatment is complete or nearly complete tumor excision.<sup>8</sup> In type II or type III tumors that cannot be completely removed, radiotherapy can be performed additionally, or alone. Furthermore, temozolomide chemotherapy can also be preferred in malignant meningiomas.

### **Method**

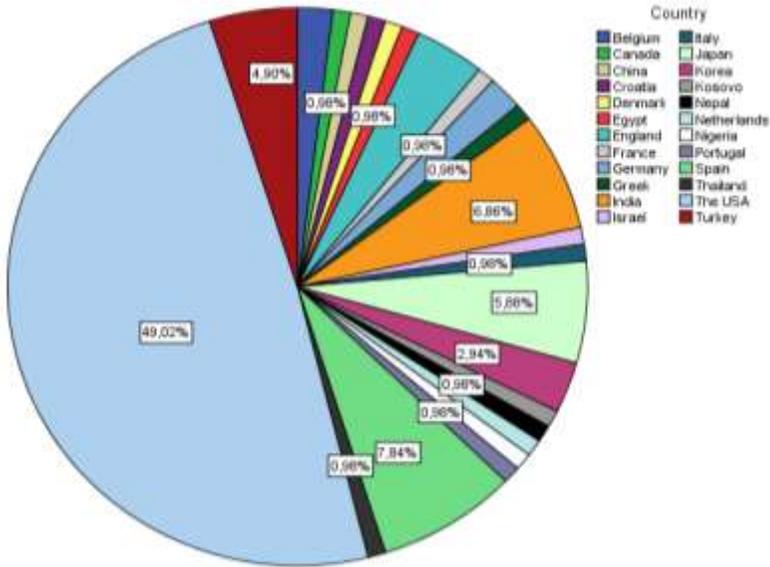
A total of 102 case reports, which met the criteria for cutaneous meningioma used today and were obtained through the literature

review conducted through various international search directories, particularly PubMed, were reviewed. Clinical, macroscopic, microscopic and immunohistochemical findings of cutaneous meningioma cases were examined. These findings were recorded in an Excel table. The data obtained from these Excel tables were processed with SPSS software and the relationship between the findings was investigated.

Parametric values were expressed as mean and standard deviations, while nominal and ordinal values were expressed as frequency analysis. Kolmogorov Smirnov test was used for normality analysis. In the analysis of normal scale parameters, Independent T-test was used for two group differences and one-way analysis of variance (ANOVA) was used for more group differences. In the analysis of nonparametric scale parameters, Mann Whitney U test was used for two group differences and Kruskal Wallis Test was used for more group differences. Chi-Square, Likelihood ratio and Fisher's Exact tests were used for differences of nominal and ordinal parameter differences. All analyses were performed at SPSS version 17.0 for Windows at a 95% confidence interval.

## **Results**

A total of 102 cutaneous meningioma case reports reported in the literature were reviewed. Most of these 102 cases (49.02%) were reported from America. The remaining cases were reported from Spain (7.84%), India (6.86%), Japan (5.88%), Turkey (4.9%), Korea (2.94%), the UK (2.94%), Belgium (1.96%) and other countries (17.66%), respectively (Graph 1).



**Graph 1:** Countries where case reports are reported from.

The ages of 102 patients ranged from 0 to 82 years. The mean age was  $32.68 \pm 24.35$  years. Three case reports did not specify the sex of the patients. Of the 99 cases, 43 (43.4%) were female and 56 (56.6%) were male and there was no statistically significant difference between them. The male to female ratio was 1.3:1. The maximum diameter of the tumor at the time of diagnosis ranged from 0.2 to 22.5 cm. The largest tumor diameter was  $3.64 \pm 3.52$  cm. The duration of the tumor in the body ranged from one to two weeks to 35 years. Mean duration of tumor in the body was  $10.60 \pm 10.56$  years. At the time of diagnosis, 18 (18.2%) patients had a concomitant intracranial meningioma, seven (6.9%) patients had a history of previous head trauma, seven (6.9%) patients had a bone defect, eight (7.8%) patients had immobility, nine (8.8%) patients had neurological findings, and 18 (17.6%) patients had malignancy (Table 1).

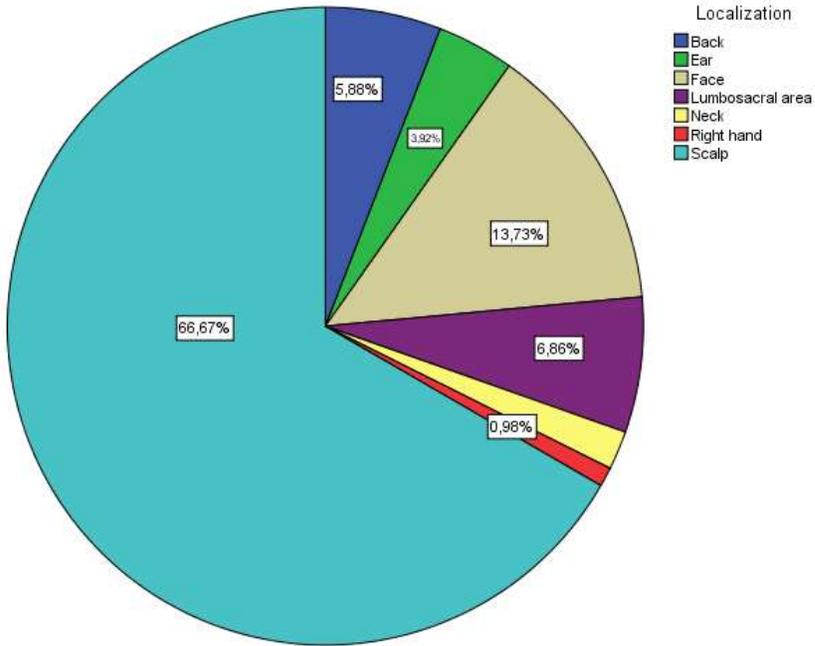
**Table 1:** Various clinical features of cutaneous meningiomas.

	Cutaneous Meningiomas
Age, Mean $\pm$ SD	$32.68 \pm 24.35$
Male	56 (56.6%)
Female	43 (43.4%)
Male to Female ratio	1.3:1
Largest Tumor Diameter, Mean $\pm$ SD	$3.64 \pm 3.52$

Duration of tumor, Mean±SD	10.60±10.56
Association of Intracranial Meningioma, n (%)	18 (18.2%)
Head trauma, n (%)	7 (6.9%)
Bone defect, n (%)	7 (6.9%)
Palpation sensitivity, n (%)	8 (7.8%)
Presence of immobile tumor, n (%)	8 (7.8%)
Presence of neurological findings n (%)	9 (8.8%)
Presence of malignancy, n (%)	18 (17.6%)

Of the 102 cutaneous meningiomas, 68 (66.67%) were located on the scalp. The remaining 14 (13.73%) was located on the face, seven (6.86%) in the lumbosacral region, six (5.88%) on the back, four (3.92%) in the ear, two (1.96%) on the neck, and one (0.98%) on the fifth finger of the right hand (Ghraph 2).

Cutaneous meningioma cases were more common in the scalp. They were mostly seen in the occipital region of the scalp. They were seen in the parietal, frontal, vertex and temporal scalp, respectively. Scalp was followed by the face, lumbosacral region, back, ear, neck and fifth finger of the right hand (Ghraph 2).



Graph 2: Localization of cutaneous meningiomas.

Type classification of 90 of 102 cutaneous meningiomas could be performed. Of these 90 cutaneous meningiomas, 51 (56.7%) were Type I, 21 (23.3%) were Type III and 18 (20.0%) were Type II cutaneous meningiomas (Table 2).

**Table 2:** Type classification distribution of cutaneous meningiomas.

Cutaneous Meningiomas	n%
Type I	51 (56.7%)
Type II	18 (20.0%)
Type III	21 (23.3%)

Fourteen (13.7%) of the cutaneous meningioma patients had a history of previous meningioma surgery. When the mean age of these cases is examined, the mean age of the patients with a history of previous meningioma surgery ( $60.43 \pm 9.44$ ) was found to be statistically significantly higher ( $p=0.000$ , Table 3) than the mean age of cases without previous meningioma surgery ( $28.27 \pm 23.06$ ).

In addition, the presence of concomitant intracranial meningioma (relapse) in cutaneous meningioma patients with a history of previous meningioma surgery (57.1%) was statistically significantly higher

than the presence of concomitant intracranial meningioma (11.8%) in cutaneous meningioma cases without a history of previous meningioma surgery ( $p=0.000$ , Table 3).

The presence of neurological findings (28.6%) in cutaneous meningioma cases with a history of previous meningioma surgery was also statistically significantly higher than that of cutaneous meningioma cases (5.7%) without a history of meningioma surgery ( $p=0.017$ , Table 3).

The presence of malignant meningioma (42.9%) in cutaneous meningioma cases with a history of previous meningioma surgery was statistically significantly higher than that of cutaneous meningioma cases (13.6%) without a history of meningioma surgery ( $p=0.018$ , Table 3).

**Table 3:** Significant clinical features of cutaneous meningiomas with a history of previous meningioma surgery.

	No history of meningioma surgery n=88	Had a history of meningioma surgery n=14	P
Age, Mean $\pm$ SD	28.27 $\pm$ 23.06	60.43 $\pm$ 9.44	0.000 <sup>a</sup>
Presence of concomitant intracranial meningioma	10 (11.8%)	8 (57.1%)	0.000 <sup>a</sup>
Presence of neurological findings	5 (5.7%)	4 (28.6%)	0.017 <sup>d</sup>
Presence of malignancy	12 (13.6%)	6 (42.9%)	0.018 <sup>d</sup>

a. Mann Whitney U Test, b. Independent Samples T-Test, c. Chi-Square Test, d. Chi-Square Test (Likelihood ratio), e. Fisher's Exact Test

As a result, cutaneous meningioma cases with a history of previous meningioma surgery (which may be Type I, Type II or type III) were seen in the elderly, approximately half had a relapse, approximately one quarter has developed neurological deficits and half has developed and relapsed malignant meningiomas (Table 3).

Type classification was managed to do in 13 of 14 cutaneous meningioma cases with a history of previous meningioma surgery. In one of those, type distinction absolutely could not be made (could be type II or type III). Of these 13 cutaneous meningioma cases, 11 (84.6%) were Type III cutaneous meningiomas, while the remaining 2 (15.4%) were type II cutaneous meningiomas. Meningioma surgeries performed in two type II cutaneous meningiomas were incomplete type II cutaneous meningioma excisions performed at the same area and they had relapse. However, there was a history of intracranial

meningioma surgery in 11 type III cutaneous meningiomas. In 11 of 88 cutaneous meningioma cases without a history of previous meningioma surgery, type distinction could not be made exactly. However, type classification was made in 77 patients. Of the 77 cutaneous meningioma cases in which type classification was performed, 51 (66.2%) were Type I cutaneous meningiomas, 14 (18.2%) were Type II and 12 (15.6%) were type III cutaneous meningiomas (p=0.000, Table 4).

As a result, there was no relapse in Type I cutaneous meningiomas. The relapse rate was observed as 15% in type II cutaneous meningiomas. There was a history of previous intracranial meningioma in type III cutaneous meningioma cases. They had no cutaneous meningiomas previously. Especially in craniotomy areas, secondary to intracranial meningioma surgery, cutaneous meningiomas have developed at a rate of 85% (Table 4).

**Table 4:** Type classification distribution of cutaneous meningiomas with a history of previous meningioma operation.

Type, n (%)	No history of meningioma surgery n=77	Had a history of meningioma surgery n=13	p
Type I	51 (66.2%)	-	0.000 <sup>d</sup>
Type II	14 (18.2%)	2 (15.4%)	
Type III	12 (15.6%)	11 (84.6%)	

a. Mann Whitney U Test, b. Independent Samples T-Test, c. Chi-Square Test, d. Chi-Square Test (Likelihood ratio), e. Fisher's Exact Test

Of those, the mean age of the congenital ones at the time of diagnosis was (13.27±10.06) and was significantly lower than the mean age of acquired ones (Type II or Type III) at diagnosis (51.35 ± 18.78 ) (p=0.000, Table 5).

The largest tumor diameter at the time of diagnosis in congenital ones was (2.64±1.63), and was significantly smaller than the largest tumor diameter (4.68±4.55) at the time of diagnosis in acquired ones (Type II or Type III) (p=0.019, Table 5).

The length of stay of the tumor in the body at the time of diagnosis of congenital ones was (13.27±10.06) and it was significantly longer than the length of stay of the tumor in the body at the time of diagnosis of acquired ones (Type II or Type III) (4.81±9.37) (p=0.001). This finding shows that as the congenital Type I meningiomas are benign and small in size and do not cause much

discomfort to the patient, they are operated after a longer time, compared to acquired Type II and Type III meningiomas (Table 5).

The presence of bone defects (12.0%) in 50 congenital cutaneous meningiomas (Type I) was statistically significantly higher than the presence of bone defects (1.9%) in 52 acquired cutaneous meningiomas (Type II or Type III) (p=0.050, Table 5).

The presence of fixed tumor (0.0%) in 50 cases of congenital cutaneous meningioma (Type I) was statistically significantly lower than the presence of fixed tumor (15.4%) in 52 cases of acquired cutaneous meningioma (Type II or Type III) (p=0.002, Table 5).

**Table 5:** Significant clinical features of congenital and acquired cutaneous meningiomas.

	Acquired (Type II and Type III) n=52	Congenital (Type I) n=50	p
Age, Mean ± SD	51.35±18.78	13.27±10.06	0.000 <sup>a</sup>
Largest Tumor Diameter, Mean ± SD	4.68±4.55	2.64±1.63	0.019 <sup>a</sup>
Tumor Duration, Mean ± SD	4.81±9.37	13.27±10.06	0.001 <sup>b</sup>
Presence of bone defect, n (%)	1 (1.9%)	6 (12.0%)	0.050 <sup>e</sup>
Presence of fixed tumor, n (%)	8 (15.4%)	-	0.003 <sup>e</sup>
Presence of neurologic findings, n (%)	9 (17.3)	-	0.002 <sup>e</sup>
Presence of malignancy, n (%)	18 (34.6%)	-	0.000 <sup>d</sup>

a Mann Whitney U Test, b. Independent Samples T-Test, c. Chi-Square Test, d. Chi-Square Test (Likelihood ratio), e. Fisher's Exact Test

The presence of neurological findings (0.0%) in 50 cases with congenital cutaneous meningiomas (Type I) was statistically significantly lower than the presence of neurological findings (17.3%) in 52 acquired cutaneous meningiomas (Type II or Type III) (p=0.002, Table 5).

The presence of malignancy (0.0%) in 50 cases with congenital cutaneous meningioma (Type I) was statistically significantly lower than the presence of malignancy (34.6%) in 52 acquired cutaneous meningiomas (Type II or Type III) (p=0.000, Table 5).

As a result, congenital (Type I) cutaneous meningiomas are seen and operated at a younger age than acquired (Type II and Type III)

cutaneous meningiomas. Tumor diameters at the time of diagnosis were smaller, length of stay in the body (time to operation) was longer and bone defects were seen more common. In congenital (Type I) cutaneous meningiomas, there were no fixed tumors, neurological findings and malignancies (Table 5).

The localization of the congenital ones (type I) of cutaneous meningiomas was mostly in vertical scalp, occipital scalp, neck, back, lumbosacral region, whereas acquired ones were mostly located in frontal scalp, ear, parietal scalp, temporal scalp, face and right hand. These localizations were statistically significantly different ( $p=0.000$ , Table 6).

**Table 6:** The localization distribution of congenital and acquired cutaneous meningiomas.

Localization, n (%)	Acquired (Type II and Type III) n=52	Congenital (Type I) N=50	p
Occipital Scalp	6 (11.5)	12 (24.0)	0.000 <sup>d</sup>
Back	-	6 (12.0)	
Neck	-	2 (4.0)	
Right hand	1 (1.9)	-	
Frontal Scalp	10 (19.2)	1 (2.0)	
Ear	4 (7.7)	-	
Parietal Scalp	14 (26.9)	4 (8.0)	
Vertex Scalp	2 (3.8)	8 (16.0)	
Temporal Scalp	3 (5.8)	-	
Scalp	3 (5.8)	5 (10.0)	
Face	9 (17.3)	5 (10.0)	
Lumbosacral Region	-	7 (14.0)	

a Mann Whitney U Test, b. Independent Samples T-Test, c. Chi-Square Test, d. Chi-Square Test (Likelihood ratio), e. Fisher's Exact Test

The mean age of 7 cutaneous meningioma cases with head trauma was  $51.86 \pm 17.13$  and it was statistically significantly higher than the mean age of 95 cutaneous meningioma cases without head trauma ( $31.27 \pm 24.27$ ) ( $p=0.026$ , Table 7).

In 7 cases of cutaneous meningioma with head trauma, the duration of stay of the tumor in the body at the time of diagnosis was  $5.17 \pm 4.44$  and it was statistically significantly lower than of that in 95 cases of cutaneous meningioma without head trauma ( $11.09 \pm 10.82$ ) ( $p=0.022$ ). This shows that head trauma-induced cutaneous meningiomas grow faster and are noticed more rapidly (Table 7).

The presence of neurological findings in 7 cutaneous meningioma cases with head trauma was 42.9% and it was statistically significantly higher than the presence of neurological findings in 95 cutaneous meningioma cases without head trauma (6.3%) ( $p=0.014$ , Table 7).

**Table 7:** Significant clinical features of cutaneous meningiomas with a history of head trauma.

	No history of Head trauma, n=95	Had a history of trauma, n=7	p
Age, Mean $\pm$ SD	31.27 $\pm$ 24.27	51.86 $\pm$ 17.13	0.026 <sup>a</sup>
Tumor Duration, Mean $\pm$ SD	11.09 $\pm$ 10.82	5.17 $\pm$ 4.44	0.022 <sup>b</sup>
Presence of neurologic findings	6 (6.3%)	3 (42.9%)	0.014 <sup>e</sup>

a. Mann Whitney U Test, b. Independent Samples T-Test, c. Chi-Square Test, d. Chi-Square Test (Likelihood ratio), e. Fisher's Exact Test

Seven (100%) of 7 cutaneous meningioma cases with head trauma in which type classification were performed were Type II cutaneous meningiomas. Of 83 cutaneous meningioma cases with no history of head trauma in which type classification were performed, 51 (61.4%) were Type I cutaneous meningioma, while 22 (26.5%) were Type III and 10 (12.0%) were type II cutaneous meningioma ( $p=0.000$ ). This finding shows that head trauma-induced cutaneous meningiomas are Type 2 cutaneous meningiomas (Table 8).

The duration of stay of the tumor at the time of diagnosis in 7 cutaneous meningioma cases with the bone defect was  $19.33 \pm 5.57$  and it was statistically significantly longer in 95 cutaneous meningioma cases without the bone defect ( $9.82 \pm 10.57$ ) ( $p=0.034$ , Table 9).

**Table 8:** Type classification distribution of cutaneous meningiomas with a history of head trauma.

Type, n (%)	No history of head trauma, n=95	Had a history of head trauma, n=7	p
Type I	51 (61.4%)	-	0.000 <sup>d</sup>
Type II	10 (12.0%)	7 (100%)	
Type III	22 (26.5%)	-	

a. Mann Whitney U Test, b. Independent Samples T-Test, c. Chi-Square Test, d. Chi-Square Test (Likelihood ratio), e. Fisher's Exact Test

It was not possible to classify 12 of 102 cases according to the classification of Lopez et al. No decision was made between the two types. Of 90 cutaneous meningioma cases whose types could be classified, the mean age of 51 Type I cutaneous meningioma cases was  $13.24 \pm 9.96$ , the mean age of 18 Type II cutaneous meningioma cases was  $49.25 \pm 14.81$ , and the mean age of 21 Type III cutaneous meningioma cases was  $59.13 \pm 16.50$ . The mean age of type I, type II and type III was statistically significantly different from each other ( $p=0.026$ ). The higher the type number, the higher the mean age (Table 10).

**Table 9:** The duration of stay of the tumor at the time of diagnosis in cutaneous meningiomas with and without bone defects

	Had a history of bone defect no n=95	Had a history of Bone defect n=7	p
Tumor Duration, Mean $\pm$ SD	9.82 $\pm$ 10.57	19.33 $\pm$ 5.57	0.034 <sup>b</sup>

a. Mann Whitney U Test, b. Independent Samples T-Test, c. Chi-Square Test, d. Chi-Square Test (Likelihood ratio), e. Fisher's Exact Test

Of the 90 cutaneous meningioma cases whose types can be classified, the mean diameter of the largest tumor at the time of diagnosis of 51 Type I cutaneous meningioma cases was  $2.61 \pm 1.62$ , of 18 Type II cutaneous meningioma cases was  $4.08 \pm 3.24$ , and of 21 Type III cutaneous meningioma cases was  $6.09 \pm 5.79$ . The mean diameter of the largest tumor of type I, type II and type III at the time of diagnosis were statistically significantly different from each other ( $p=0.006^a$ ). The higher the type number, the higher the mean diameter of the largest tumor at the time of diagnosis (Table 10).

Of 90 cutaneous meningioma cases whose types could be classified, the rate of the presence of the fixed tumor was 0.0% in 51

Type I cutaneous meningioma cases, 11.1% in 18 Type II cutaneous meningioma cases, and 14.3% in 21 Type III cutaneous meningioma cases. The fixed tumor presence rate of type I cutaneous meningiomas was statistically significantly lower than the fixed tumor presence rates of type II and type III cutaneous meningiomas ( $p=0.013$ ). There was no fixed tumor in type I cutaneous meningiomas (Table 10).

Of the 90 cutaneous meningioma cases whose types could be classified, the rate of the presence of neurological findings was 0.0% in 51 Type I cutaneous meningioma cases, 11.1% in 18 Type II cases, and 23.8% in 21 Type III cases. The presence rate of neurological findings of type I, type II and type III cutaneous meningiomas were statistically significantly different from each other ( $p=0.001$ ). The higher the type number, the higher the rate of the presence of neurological findings. There were no neurological findings in any of type I cutaneous meningiomas (Table 10).

Of the 90 cutaneous meningioma cases whose types can be classified, the presence of malignancy was 0% (0 cases) in 51 type I cutaneous meningioma cases, was 0% (0 cases) in 18 type II cutaneous meningioma cases, and was 73.9% (17 cases) 21 type III cutaneous meningioma cases, respectively. The rate of the presence of malignancy between type I and type II and type III cutaneous meningiomas was statistically significantly different from each other ( $p=0.001$ ). All malignant cases were type III cutaneous meningiomas. All Type I and Type II cutaneous meningiomas were benign (Table 10).

**Table 10:** Significant clinical features of Type I, Type II and Type III cutaneous meningiomas.

	Type I (n=51)	Type II (n=18)	Type III (n=21)	P
Age, Mean $\pm$ SD	13.24 $\pm$ 9.96	49.25 $\pm$ 14.81	59.13 $\pm$ 16.50	0.000 <sup>a</sup>
Largest Tumor Diameter, Mean $\pm$ SD	2.61 $\pm$ 1.62	4.08 $\pm$ 3.24	6.09 $\pm$ 5.79	0.006 <sup>a</sup>
Presence of fixed tumor, n (%)	-	2 (11.1%)	3 (14.3%)	0.013 <sup>d</sup>
Presence of neurologic findings, n (%)	-	2 (11.1%)	5 (23.8%)	0.001 <sup>d</sup>
Malignant, n (%)	-	-	19 (90.5%)	0.001 <sup>d</sup>

a. Mann Whitney U Test, b. Independent Samples T-Test, c. Chi-Square Test, d. Chi-Square Test (Likelihood ratio), e. Fisher's Exact Test

**Table 11:** Immunohistochemical properties of cutaneous meningiomas.

Immunohistochemical stains	Positive	Negative	Total
Vimentin	32 (100.0%)	-	32
EMA	38 (90.5%)	4 (9.5%)	42
PR	7 (100%)	-	7
S-100	7 (19.4)	29 (80.6)	36
Cytokeratin AE1/AE3	4 (12.9%)	27 (87.1)	31
NSE	1 (12.5)	7 (87.5)	8
Desmin	1 (9.1)	10 (90.9)	11
NF	1 (50.0)	1 (50.0)	2
CD34	-	13 (100.0)	13
SMA	-	12 (100.0)	12
CD31	-	11 (100.0)	11
Factor-VIII	-	9 (100.0)	9
GFAP	-	8 (100.0)	8
CD68	-	7 (100.0)	7
HMB-45	-	6 (100.0)	6
Chromoginin-A	-	5 (100.0)	5
Synaptophysin	-	4 (100.0)	4
Melan-A	-	3 (100.0)	3
Factor-XIIIa	-	2 (100.0)	2
TFF-1	-	2 (100.0)	2
ERG	-	2 (100.0)	2
$\alpha$ -1-Antitrypsin	-	1 (100.0)	1
CEA	-	1 (100.0)	1
ER	-	1 (100.0)	1
CD56	-	1 (100.0)	1
CD-99	-	1 (100.0)	1

Immunohistochemical examination was performed to confirm the diagnosis in some of these 102 cutaneous meningiomas. According to the results of these immunohistochemical studies, the dyeing was observed with vimentin 100% (32/32), EMA 90.5% (38/42), PR 100% (7/7), S-100 protein 19.4% (7/36), cytokeratin AE1/AE3 12.9 % (4/31), NSE 12.5% (1/8), desmin 9.1% (1/11) and NF 50% (1/2). Apart from these, no dyeing was observed in tumor cells with CD34 (0/13), SMA (0/12), CD31 (0/11), factor-VIII (0/9), GFAP (0/8), CD68 (0/7), HMB-45 (0/6), chromogranin-A (0/5), synaptophysin (0/4), melan-A (0/3), factor-XIIIa (0/2), TTF-1 (0/2), ERG (0/2),  $\alpha$ -1-Antitrypsin (0/1), CEA (0/1), ER (0/1), CD56 (0/1), CD99 (0/1), somatostatin (0/1), STAT- 6 (0/1), MSA (0/1), CK7 (0/1), CK5/6 (0/1), p63 (0/1), PSA (0/1), PSAP (0/1) , LCA (0/1), CD10 (0/1) (Table 11).

### **Conclusions**

Cutaneous meningiomas are approximately equal in men and women. They are most commonly seen on the scalp. It is followed by the face, lumbosacral region, back, ear, neck region in turn. One case was reported in the 5th finger of the right hand. The most common type of cutaneous meningiomas is type I cutaneous meningiomas.

Type I cutaneous meningiomas are benign. They show no recurrence. The mean operating age of type I cutaneous meningiomas was about 13 years. They are mostly seen in the first two decades. They are associated with bone defects. Type I cutaneous meningiomas are small and their the average diameter is 2.5 cm.

Type II meningiomas are associated with skull fractures. The mean operation age was about 49 years. They are mostly seen in the 3rd-5th decades. Neurological findings may occur. Type II cutaneous meningiomas are of medium size. Their the average diameter is 4 cm.

Type III meningiomas are associated with an anaplastic or atypical intracranial meningioma. The mean operation age was about 59 years. They are mostly seen in the 6th-9th decades. There are neurological findings. Type III cutaneous meningiomas are big. Their the average diameter is 6 cm.

Cutaneous meningiomas with a history of meningioma surgery are more common in elderly patients. Most of the cutaneous meningiomas with a history of meningioma surgery are Type III, with a small proportion of them being Type II. Cutaneous meningiomas with a history of meningioma surgery have a high probability of neurological findings and malignancy.

Acquired cutaneous meningiomas have larger diameters than congenital. Acquired cutaneous meningiomas are most commonly seen in parietal scalp, frontal scalp, face, occipital scalp and ear. Congenital cutaneous meningiomas are most commonly seen in occipital scalp, vertical scalp, lumbosacral area and back.

Cutaneous meningiomas with a history of head trauma are more common in elderly patients. Cutaneous meningiomas with a history of head trauma have a low probability of neurological findings. All of cutaneous meningiomas with a history of head trauma are type II cutaneous meningiomas.

Immunohistochemically, cutaneous meningiomas are usually stained with Vimentin, EMA and PR. In rare cases, staining with cytokeratin AE1/AE3, S-100 protein, NSE and desmin was also observed.

### **Suggestions**

As a general rule in pathology, tumors are named according to the tissue from which they originate. Therefore, for the diagnosis of primary skin meningioma; 1-Tumor should be located in the skin and/or subcutaneous tissue 2-Should have the typical histological structure of neuroaxis meningioma 3- Should have no neuroaxis meningioma itself or its history.

Meningiomas which are neuroaxis meningioma and thought or detected to be associated with it, should be reported as "neuroaxis meningioma and skin/soft tissue metastasis" instead of Type III cutaneous meningioma.

Type II meningiomas should not be reported as type II cutaneous meningioma, unless the amount of soft tissue tumor is less than the amount of tumor in the skin and/or subcutaneous tissue. Tumors in which the amount of tumor in the soft tissue exceeds the amount of tumor in the skin and/or subcutaneous tissue should be reported as soft tissue meningioma.

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## **Chapter XII**

# Schwannoma of the Appendix: A Systematic Literature Review

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## Background

Schwannomas; benign neurogenic tumors originating from schwann cells in the peripheral nerve sheath. They are usually seen in the head, neck, spinal cord and extremities, but are rarely seen in the gastrointestinal tract [1].

Gastrointestinal system schwannomas occur in the stomach (83%), small intestine (12%) and finally in the frequency of decreases in the colon and rectum. [2].

Schwannoma of colon and rectum occurs most frequently in the cecum and right colon (30.5%) followed by the sigmoid (28.1%), the rectum (21.1%), the left colon (8.3%), the transverse colon (5.3%), and the appendix (1.1%). The tumor size ranged from 0.3 to 28 cm with a mean of 3.78 cm (median 3 cm). [3].

Schwannomas of the appendix are rare among gastrointestinal schwannomas. They are usually discovered incidentally as a submucosal mass on routine colonoscopy and diagnosed on pathologic examination of the operative specimen. Little information exists on the diagnosis and management of this rare entity.

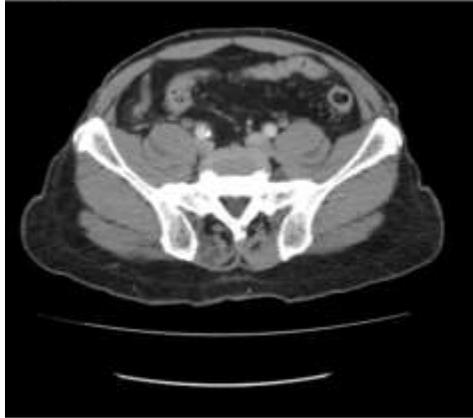
The aim of this study is to report a case of appendicular schwannoma and the results of a systematic review of appendicular schwannoma in the literature.

## Main Body Case Report

64-year-old male known history of Cardiac Stents, Implantable Cardioverter Defibrillator, Hypertension and Peptic Ulcer patient, presented to the emergency room with 1-day history of diffuse central abdominal pain that migrated to the right lower quadrant of abdomen,

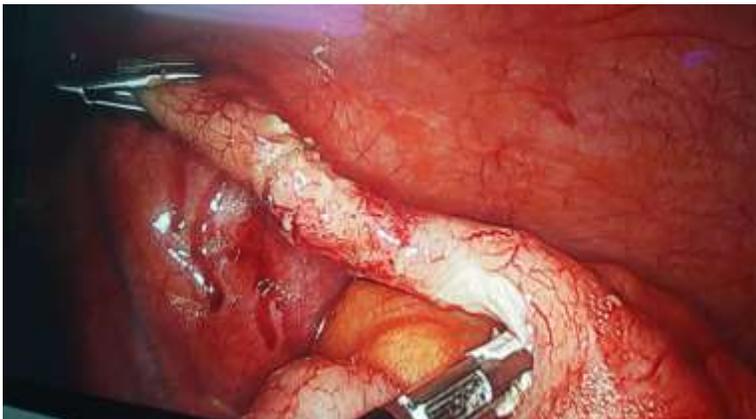
nausea and vomiting. Examination revealed signs of localized peritonism in the right lower abdomen. Laboratory examination showed no anemia (hb 13.2 g/dL) and inflammatory markers were normal except increased C-reactive protein.

No target sign consistent with appendicitis was observed on ultrasound imaging. There is a slight increase in mucosal thickness in ileal loops. But, abdominal computed tomography scan (CT scan) was observed no opaque material in the appendix, the largest diameter was 10 mm proximally and no significant inflammation was detected in periappendical fat tissue and clinical evaluation is recommended (Fig.1).



*Fig.1 No opaque material was observed in the appendix, the largest proximal diameter was measured as 10 mm.*

The patient underwent laparoscopic appendectomy with the diagnosis of acute appendicitis (Fig.2).



*Fig.2 Intraoperative appearance of appendix*

Patient was discharged on the first postoperative day. After that, finally pathology was interpreted as 1x0.4x0.3 cm schwannoma in the distal part of the appendix.

All of the material was followed and fibroblasts, eosinophils and dense schwannoma cells and appendix were obliterated especially in distal areas.

The patient was evaluated by multidisciplinary team and postoperative PET CT, endoscopy, colonoscopy and abdominal CT imaging were performed.

At 2-year follow-up, the patient is disease free.

### **Discussion**

Gastrointestinal (GI) schwannomas are rare mesenchymal tumors reported by Daimaru, who first described a schwannoma as the presence of a primary GI tumor based on positive S-100 immunostaining [4,5]. GI schwannomas are clinically important because they are distinctly different from conventional soft tissue and central nervous system schwannomas, some of which may be associated with neurofibromatosis 2.

Neurogenic tumors usually grow very slowly and the symptoms are ambiguous and specific, the common symptoms are abdominal pain, a palpable mass and bleeding; however, bowel obstruction is rare [6]. Bleeding in the small intestine is the most common symptom because when the tumor grows, a large amount of blood vessel in the submucosal tumor is exposed on the mucosal surface and can be easily injured [7]. 30-50% of appendicular tumors show clinical signs and symptoms similar to appendicitis, and this rate is higher for carcinoid tumors than other tumors [8,9,10].

Long-term ambiguous right lower quadrant pain, palpable mass in the right lower quadrant (5 years), as well as several cases of appendicular schwannoma presenting with typical acute appendicitis findings have been described [11,12].

Traditional imaging modalities such as CT, ultrasonography, barium enema, magnetic resonance imaging, and endoscopy are useful for tumor localization for a schwannoma diagnosis [13]. Since synchronous colon cancer is more common in appendix schwannomas, colonoscopy is also recommended during follow-up[14]. Sometimes during angiography of the mesenteric vessels, hypervascular vascular tumors can be found [15]. However, we could not distinguish between benign and malignant stromal tumors using only radiographic images.

Recent literature has shown that acute uncomplicated appendicitis can be managed nonoperatively with antibiotics only. Although a reasonable clinical response to non-operative treatment was initially reported, there was a significant recurrence rate of 20.4 percent within 1 year. In uncomplicated appendicitis treated with antibiotics, incidental tumors may be missed. [16].

An additional schwannoma is a very rare tumor. It occurs without a specific symptom and preoperative diagnosis is difficult. It is thought that complete surgical excision is the best approach and determines the overall outcome. Laparoscopic surgery, however, must have a clear resection margin for the treatment of appendicular schwannoma and its recurrence should result in an unusual prognosis; This may prevent unnecessary laparotomy.

### **Conclusions**

Colorectal schwannoma is a very rare subtype of gastrointestinal schwannoma which occurs in the elderly, almost equally in men and women. Schwannoma should be included in the differential diagnosis of a submucosal lesion along with gastrointestinal stromal tumor, neuro-endocrine tumors, and leiomyoma-leiomyosarcoma. Definitive diagnosis is based on immunohistochemistry of the operative specimen. Rarely malignant, surgery is the mainstay of treatment.

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## **Chapter XIII**

# Scapular winging due to scapular osteochondroma with accessory nerve involvement

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We report on a 29-year-old male patient, who presented at our clinic with scapula alata on the right side. The patient also complained of shoulder discomfort, however range of motion of right shoulder was found to be normal. The patient had unremarkable medical and family histories.

There was history of gradually increasing asymmetry of upper back for last 2–3 months.

In neurological status, we found asymmetry of right upper back with scapular winging, with mild trapezius muscle atrophy.

Electrodiagnostic studies, electromyography and nerve conduction studies, showed mild right accessory nerve (XI) compression.

Right shoulder and thoracic radiological series were indicated and registered kyphoscoliotic deformity of the mid-thoracic spine.

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A right shoulder computed tomography was performed and described a 1.4cm, X 0.3cm solid bone mass at the scapula. The diagnosis of an osteochondroma was stated. A magnetic resonance imaging (MRI) including the right shoulder and scapula confirmed the osteochondroma. (Figure 1)

According to the recommendations, due to local compression of XI nervous the operation was recommended to our patient but he refused it.

**Discussion:** Osteochondroma or solitary exostosis is an hamartoma that develops during growth by enchondral ossification covered with a cartilaginous cap. It represents 20 to 40% of benign bone tumors and 8 to 15% of all bone tumors. Only 6.4% of all solitary exostoses are located at the scapula. Benign lesions like osteochondroma of scapula may cause winging of scapula. This location of osteochondroma is propitious to affect the surrounding neurologic structures, mainly the suprascapular and accessory nerves. [1, 2]

Winging of the scapula (scapula alata) is defined as the prominence of the medial border of the scapula.[3].The differential diagnosis of winged scapula can be complicated .

Kyphoscoliotic deformity of the upper or mid-thoracic spine may also present with similar clinical findings with pseudowinging.

Some authors suggest that diagnostic evaluation in all cases of scapular deformity should include electromyography and nerve conduction studies as both diagnostic and prognostic procedure [4].

Scapular osteochondroma is not always visible on plain radiograph. CT is not only helpful for confirming the diagnosis but also for therapy planning. MRI is recommended if malignancy is suspected and to confirm the diagnosis. MRI visualizes the effect of the lesion on surrounding structures. A bone scintigraphy and as biopsies are less common applied in diagnostic of the osteochondroma. The prognosis of osteochondroma is excellent. Resection of the osteochondroma is the treatment of choice for winged scapula caused by an exostosis. Operative treatment is recommended in the case of pain, decreased range of motion of the shoulder or local compression of nervous or vascular structures [4,5]

In conclusion, this patient is presented to illustrate the clinical course and radiographic findings for this rare condition. Due to its rarity of presentation may cause as well as in our case diagnostic dilemma and challenge of correct diagnosis and treatment.

## Compliance with ethical standards

**Conflict of interest:** The authors of this manuscript comply with the Principles of Ethical Publishing and have no conflict of interest.

**Ethical approval:** This manuscript does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent:** Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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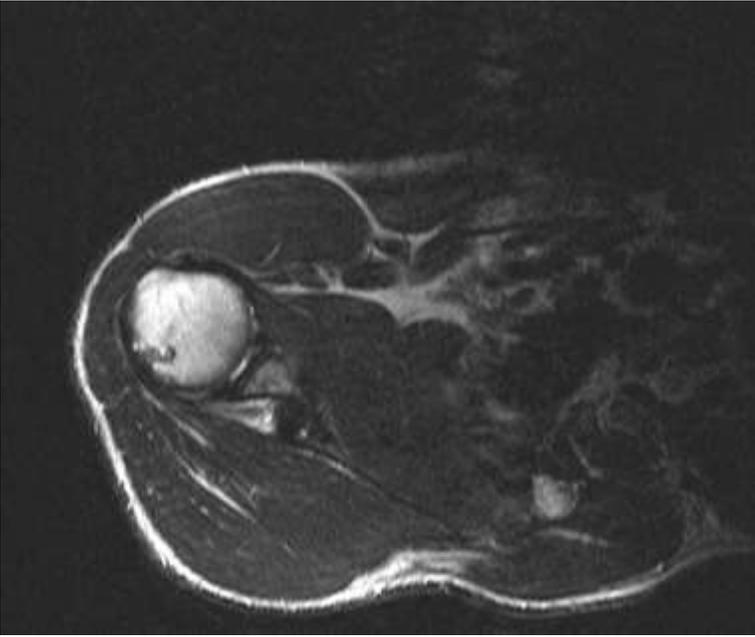


Figure 1. Thoracic MR imaging of the osteochondroma- T1 axial view (a) showing the scapular osteochondroma measuring 1.4cm.

## **Chapter XIV**



# Aggressive vertebral hemangioma as unusual cause of paraparesis – a case from Southeast Europe

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## Case Presentation

A 65-year-old male patient, with completely normal medical history, came to the our Emergency Department at Clinical Hospital of Traumatology (Zagreb, Republic of Croatia) with symptoms of back pain, bilateral lower-extremity weakness and numbness, with progressive deterioration during the last ten days. He had no fever, headache and bowel/bladder symptoms. In neurological status, we found billateral reduction of quadriceps strength (3/5) and ankle dorsiflexion (2/5).

Radiological plain examination revealed a degenerative changes of the thoracic spine and collapse of the 7th thoracal vertebra (Th7). MRI evaluation has shown an avidly enhancing mass within the body and right transverse process of the Th7, with extension into the posterolateral epidural space. The consequent spinal cord compression resulted with myelopathy (Figures 1 and 2).

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Regarding to the destructive tumor characteristics and clinical picture, our patient had indication for neurosurgery procedure. After preoperative embolization (Figure 3), neurosurgeon performed decompressive Th 6-8 laminectomy, with subsequent resection of the tumor and vertebroplasty. Surgical procedure underwent without complications. Pathohistological diagnosis was epithelioid hemangioma (EH). Before discharge from the hospital, neurological function significantly improved. During 6-month follow-up, our patient had additional neurological improvement with residual minor spastic haemiparesis.

### **Discussion**

We presented the first case of EH (not hemangioendotelioma or pure hemangioma, which are different entities) in Southeast Europe. Other rare data were from the United States of America, Japan and Turkey, while Calderaro et al. described a case from France (1-10). EH is a mesenchymal tumor of vascular origin. Although the World Health Organization recognizes EH as a distinct neoplasm (from year 1983), it can be difficult to differentiate histologically from endothelioid hemangioendothelioma (1-3). EH arises most frequently in the skin and subcutaneous tissues of the head, neck, and distal extremities. Osseous EH has been reported most commonly in the tubular bones of the extremities (1,2). The presence of osseous EH involving the spine is less common, with a reported frequency of 11-20% (1,2,4,5).

The mean age of presentation is 35-39 years (1,3,5). A slight male predominance has been reported at 1.4:1 in the osseous form of the disease (1,3).

EH of the spine may have aggressive local features and may present with pain or neurological impairment secondary to instability. An extraosseous component may be present, which can significantly contribute to neurological compromise, given the rigid anatomical boundaries of the spinal canal. Osseous destruction by EH can cause instability or pathologic fractures, also leading to neurologic impairment. This can lead to an acute or chronic presentation (1,2).

The radiographic appearance is most typically that of a lytic, well-defined lesion on plain film or CT. The MRI appearance is typically hypointense on T1WI, hyperintense on T2WI, and avidly enhancing, often with an extraosseous soft-tissue component (1-5).

Optimal treatment management of EH within the spine is still an area of research. A combination of en bloc resection, curettage, pre/postoperative embolization, radiation, and observation has been

used with success (1,2). Local recurrence was reported in 11% of patients, in a series of 36 patients (1,3). Imaging surveillance is often recommended for this reason.

### **Conclusion**

Our case report suggests that EH of the spine can be locally aggressive with destruction of the adjacent bone cortex and with soft-tissue extension. The rarity of the tumor and non-specific clinical presentations adds to the challenge of early correct diagnosis and treatment.

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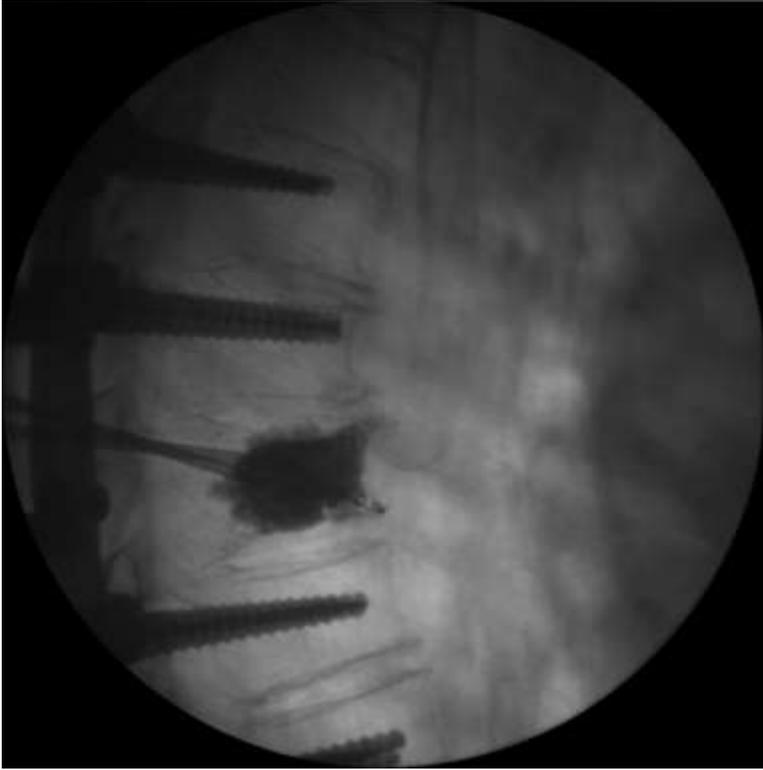
## FIGURES



**Figure 1.** MRI evaluation: Th7 vertebral body lesion with enhancing mass, extending into the posterolateral epidural space, with low signal intensity on T1-weighted images. The spinal cord is displaced and compressed (marked with arrow).



**Figure 2.** MRI evaluation: a mass with high signal intensity on T2-weighted images (marked with arrow).



**Figure 3.** Postoperative lateral radiograph obtained after decompressive laminectomy and vertebroplasty, showing cement filling the residual vertebral body, which was involved in tumor. Coils from the preoperative embolization can also be seen here.