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The contribution of preoperative MRI evaluation to emergency surgical management of perianal abscesses

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ABSTRACT

Objective: Perianal abscesses occur as a result of an infection in the anal gland due to the obstruction of the anal gland ducts opening to the anal crypts. Preoperative use of MRI reduces the risk of recurrence, fistula formation, and postoperative fecal incontinence as it allows detailed anatomical imaging. This study aims to investigate the contribution of preoperative MRI to reducing recurrence and surgical complications in patients who underwent emergency surgery for perianal abscess.

Material and Methods: A total of 206 patients with perianal abscesses evaluated and not evaluated with MRI between January 2016 and 2021 were included in this retrospective study. The patients had no history of surgery or local drainage applied to the perianal region. In addition to demographic data of patients, postoperative complications, hospitalization duration, recurrence ratio, and MRI findings were evaluated.

Results: During the preoperative period, recurrence was found in 16 (13.2%) out of 121 cases that were evaluated with MRI, while the disease recurred in 24 (28.2%) out of 85 cases that were operated on without MRI evaluation. The presence of a fistula was significantly higher, while the presence of recurrence was significantly lower in the group that underwent MRI in the preoperative period (p=0.033, p=0.012, respectively).

Conclusion: Contrary to popular belief, surgical treatment of abscesses is not that easy due to the high risk of recurrence, the high rate of association with perianal fistula, and the different types and spreads of abscesses. Therefore, preoperative MRI is the most useful diagnostic method for detecting perianal abscesses and additional pathologies.

Keywords: Perianal abscess, Magnetic Resonance Imaging, Surgery

INTRODUCTION

Perianal abscesses are one of the common and problematic diseases of the anus and rectum region. Infection most commonly occurs due to a blocked anal crypt gland. Pus accumulates in the subcutaneous tissue where perianal abscesses occur, in the intersphincteric plane, and in the ischiorectal or supralevator areas. Perianal abscesses should be surgically drained as soon as they are diagnosed. If the abscess is not drained, it tends to rapidly expand into adjacent anatomical areas as well as progress to widespread systemic infection.

Perianal abscesses and fistulas are two consecutive stages of the same infectious process. Abscess formation, suppuration, and fistulization stages constitute the acute phase of the infection, while fistulization constitutes the chronic phase (1). Therefore, it is usual for 30-70% of perianal abscesses to be associated with a concomitant fistula and for 30-40% of patients to experience a fistula complication after treatment for a perianal abscess (1, 2). For all these reasons, evaluating patients with optimal imaging methods is essential, especially before the first surgery and during the follow-up period. Magnetic Resonance Imaging (MRI) contributes significantly to the diagnosis and guides the surgical plan by revealing occult abscesses and secondary fistulas that can cause high recurrence after surgery and are challenging to detect in clinical examination.

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It helps to predict and prevent the possibility of postoperative fecal incontinence by showing the exact anatomical location of the perianal abscess and fistula if present. MRI is the imaging method that best demonstrates the relationship between the fistula and the anal sphincter complex by enabling detailed anatomical imaging. Coronal, axial, and sagittal MR imaging provides detailed mapping of the lines and provides easy orientation in operation (2).

This study investigated the contribution of preoperative MRI evaluation to the reduction of recurrence and surgical complications in patients who underwent emergency surgery for the perianal abscess.

MATERIALS AND METHODS

A retrospective cohort study was designed to compare patients who were diagnosed with a perianal abscess in our Emergency Surgery outpatient clinic, evaluated with MRI during the preoperative period, and operated on without MRI evaluation, in terms of recurrence and surgical complications, between January 01, 2016, and January 01, 2021. Demographic characteristics of the patients, postoperative complications, length of hospital stay, and recurrence rates and frequencies were analyzed. Furthermore, definite postoperative diagnosis, MRI findings, and preoperative physical examination findings were examined. Secondary appendages, physical examination findings of abscesses, and MRI results were compared with postoperative diagnosis in patients with complicated perianal fistula.

Patients over 18 years of age, who had not undergone any previous surgical intervention on the perianal region, and who signed the informed consent form were included in this study. Patients with a perianal abscess who underwent outpatient drainage with only local anesthesia, patients diagnosed with hidradenitis suppurativa, and primary malignancy in the perianal region were excluded. All patients were informed about MRI and possible complications. MRI was performed with the protocol specified for this study. Magnetic resonance imaging was performed using 3 Tesla MRI device (Siemens, Magnetom Vida 3T) using a standard body coil (18-channel body coil) in the supine position.

T1 weighted axial TSE (TR:510, TE:22, slice thickness 3 mm, FOV:325-350, matrix 275x320), T2 weighted TSE sagittal (TR:6000, TE:87, slice thickness 3.5 mm, FOV:265-300, matrix 256x320), T2 weighted fat suppressed TSE STIR axial (TR:3300, TE:100, slice thickness 3 mm, FOV:325-350, matrix 275x320), T2 weighted fat suppressed TSE STIR coronal (TR:3200, TE:83, slice thickness 3 mm, FOV:350-400, matrix 224x320) sequences were taken.

Precontrast and postcontrast MR images were obtained in axial, coronal and sagittal planes with and without fat suppression. A dynamic study was performed after intravenous injection of a contrast agent (Gadolinium, 0.1 mmol/kg) using T1-weighted VIBE DIXON pre- and post-contrast axial (TR:5.5, TE1:2.46, TE2:3.69, slice thickness 1 mm, FOV:325-350, matrix 180x320), T1-weighted VIBE DIXON post-contrast sagittal (TR:5.5, TE1:2.46, TE2:3.69, slice thickness 1 mm, FOV:265-300, matrix 180x320), and T1-weighted VIBE DIXON post-contrast coronal (TR:5.5, TE1:2.46, TE2:3.69, slice thickness 1 mm, FOV:350-400, matrix 261x320) sequences. MR images were evaluated by two radiologists, one with 18 years of experience and the other with five years of abdominal radiology experience (Figure 1, 2).

Statistical Analysis: For the descriptive data of the study, continuous variables were expressed as mean (Mean), standard deviation (SD), and median (median) values, and categorical variables were presented as frequencies (n) and percentages (%). Histogram, Kolmogorov-Smirnov, or Shapiro-Wilks tests were used for the normal distribution of continuous variables, and Leven's t-test evaluated group homogeneity. Age measurements of the patients were assessed with the T-test, and the length of stay was analyzed with the Mann-Whitney U tests. The chi-square test was used to examine gender, recurrence, and the presence of a fistula. Statistical analyzes were performed with the SPSS 26.0 package program, and a p<0.05 level was considered statistically significant.



Figure 1: Coronal fat-suppressed T2-weighted (a) and axial T1-weighted (b) images show a right ischioanal abscess surrounded by inflammatory changes extending superficially into the right buttock subcutaneous fat. Axial contrast-enhanced fat-suppressed T1-weighted (c) image demonstrates unilocular hypointense collection with thick and irregular enhancing capsule.



Figure 2: Coronal T2-weighted (a) and axial T1-weighted (b) images show a perianal horseshoe cystic lesion with irregular rim enhancement on axial contrast-enhanced fat-suppressed T1-weighted image (c).

RESULTS

A total of 206 patients, 163 (79.1%) male and 43 (20.9%) female, were included in this study. The mean follow-up period was 18 months. While 121 (58.7%) of 206 operated patients were evaluated with MRI preoperatively, 85 (41.3%) did not undergo an MRI examination. Recurrence was found in 16 (13.2%) of the 121 cases evaluated with MRI during the preoperative period, while the disease recurred in 24 (28.2%) of the 85 patients who were operated on without MRI evaluation. Fecal incontinence developed in only 1 (0.58%) patient. A preoperative MRI evaluation of this patient was not performed.

The mean age of 206 patients included in this study was 44.69 ± 14.39 years, and the median age was 44.0 years. There was no difference in age and gender between the groups with and without preoperative MRI (p=0.264, p=0.487). The presence of a fistula was significantly higher in the group that underwent MRI in the preoperative period (p=0.033).

Moreover, the presence of recurrence was significantly lower in the group that underwent MRI in the preoperative period (p=0.012) (Table 1). There was no difference in length of stay in the group with and without MRI in the preoperative period (p=0.176).

When the comorbidities that may pose a risk for the perianal abscess were evaluated, 42 patients (20.3%) had diabetes mellitus, 13 (6.3%) had cancer, 8 (3.9%) had morbid obesity, 7 (3.4%) had Crohn's disease, and 6 (2.9%) had HIV infection. Furthermore, there were 2 drug addicts, 2 heavy smokers, 1 alcohol addict, 1 patient with active tuberculosis, 1 patient with ulcerative colitis, 1 inpatient treatment due to Covid-19, and 1 homeless patient with very poor hygiene. There were 39 patients younger than 30 years old participating in the study. Disease recurrence was observed in 12 (30.7%) of these young patients.

Table 1. Distribution Data of Groups with and without MR imaging in the preoperative period

	All patients		Preop MRI + (n:121)		Preop MRI –(n:85)		
	Mean±SD	Median	Mean±SD	Median	Mean± SD	Median	р
Age (years)	44,69±14,39	44,0	44,65±14,61	44,0	45,22±14,50	45,0	0,264*
Length of stay (days)	$2,75\pm2,90$	2,0	3,00±3,17	2,0	$2,43\pm 2,50$	2,0	0,176**
Gender	n	%	n	%	n	%	
Male	163	79,1	98	81,0	65	76,5	0 497***
Female	43	20,9	23	19,0	20	23,5	0,407
Pre-op Fistula							
Present	68	33,0	47	38,8	21	24,7	0.022
Absent	138	67,0	74	61,2	64	75,3	0,055
Recurrence							
Present	40	19,4	16	13,2	24	28,2	0.012
Absent	166	80,6	105	86,8	61	71,8	0,012

*t-test, **Mann-Whitney U Test, ***Chi square

n: Number

SD: Standard Deviation

MRI: Magnetic Resonance Imaging

DISCUSSION

When an abscess occurs, swelling, redness, tenderness, and temperature increase may develop in the perianal region. These findings are rare in highly located supralevator abscesses, and systemic findings such as fever and malaise are more common (3). MRI should be performed to identify the presence of supralevator abscess, to enable drainage based on surgical anatomy, and to determine the relationship between abscess and anal sphincter, especially in patients presenting with anorectal sepsis that is more complex than simple perianal abscess (4). About 50% of people with a perianal abscess develop a fistula. Fistula can occur without abscess. However, the rate of fistula formation is up to 66% higher in spontaneously draining abscesses (5). The presence of an acute or chronic anal fistula can be distressing for patients and may lead to a decrease in their quality of life. Crohn's disease, cancer, trauma and radiation, and infection can increase the risk of fistulas. Treatment of perianal fistulas, which cause significant morbidity, is usually surgical. To prevent recurrence after appropriate surgical treatment, it is necessary to accurately determine the course of the fistula tract and preoperatively detect the associated secondary tract and abscesses (6). MRI is the imaging method with the highest accuracy in demonstrating these complications (7). The most important result of this study is that the presence of a fistula can be detected in patients evaluated with preoperative MRI, and the recurrence can be significantly reduced by appropriate surgical treatment in patients with perianal abscesses. In this study, as a result of revealing the pathological anatomy with MRI in the preoperative period, the presence of a fistula was detected in 47 patients, and optimal surgical treatment could be applied for fistula treatment. When 24 patients who did not undergo MRI in the preoperative period and who relapsed were examined, 21 of these patients were demonstrated to have fistulas by MRI performed later. If the recurrent cases had been evaluated with MRI before the operation, and the presence of a fistula had been detected, the number of relapsed patients could have been significantly reduced.

Approximately 10% of patients with perianal abscesses are associated with HIV, Crohn's disease, trauma, tuberculosis, sexually transmitted diseases, radiation, foreign bodies, and malignancy (8). In this study, there were 13 (6.3%) patients with cancer, 7 (3.4%) with Crohn's disease, 6 (2.9%) with HIV infection, 1 with ulcerative colitis, and 1 with active tuberculosis. consistent with the current literature. Furthermore, diabetes is a risk factor for skin infections (9). Diabetes has been particularly associated with perianal abscess formation. Also, one study concluded that the chance of the first diabetes diagnosis increased after an attack of the perianal abscess (10). In another study, a relationship was determined between diabetes and the formation of perianal abscesses, but no significant relationship was observed between diabetes and recurrence (11). However, this study was performed without distinguishing between type 1 and type 2 diabetes patients. A patient with a perianal abscess should be investigated for diabetes, as are patients with type 1 or type 2 diabetes, and particularly poorly controlled diabetes, at risk for perianal abscess.

High body mass index is an independent risk factor for perianal abscess in patients with diabetes. Although perianal abscess recurrence has been associated with obesity, this association has not been demonstrated before (11). However, studies have revealed a relationship between obesity and wound healing (12, 13). This study had 42 (20.3%) patients with diabetes mellitus and 8 (3.9%) morbidly obese patients. Recurrence developed in 5 patients with DM; 2 of these patients had uncontrolled diabetes, and one patient had morbid obesity. Four patients presented with high blood sugar and were diagnosed with DM for the first time. These findings were also compatible with the literature.

Recurrence can be significantly reduced with preoperative imaging, and surgery-related complications, such as fecal incontinence, can be less common. MRI is the imaging modality that best demonstrates the relationship between the fistula and the anal sphincter complex, allowing for detailed anatomical imaging (14). Fecal incontinence is the inability to maintain physiological control of the intestines in a socially appropriate place and time, which may include symptoms ranging from occasional involuntary gas incontinence to persistent stool incontinence (15,16). Besides, patients with fecal incontinence may be more exposed to health complications such as skin injuries and urinary tract infections (17). Fecal incontinence following the fistulectomy procedure can range from 11.5% to 20% (18). In this study, fecal incontinence complication was observed at a very low rate, only in 1 patient.

CT should be performed in patients with significant comorbidities, complex suppurative anorectal conditions, and when surgical consultation is not immediately possible. Optimal imaging may require the use of triple contrast agents and 2.5 mm sequences/slices in certain circumstances. MRI is the primary imaging modality (19). The correct diagnosis rate in the conventional fistulography method with the contrast agent used before MRI is 16% (20). Rectal and intravenous contrast-enhanced CT is unsuccessful in imaging small abscesses and fistulas due to low soft tissue resolution (21). The sensitivity of CT fistulography is high, but it is an invasive and painful method, leading to complications such as infection and sepsis (22). Primary fistula tracts are detected with an accuracy of 61% by digital examination, 81% by anal endosonography (AES), and 91% by MRI, while internal patency is detected with an accuracy of 91% with AES and 97% with MRI (23). The most common cause of the recurrent disease is the undetected spread of the infection to distant sites. When the recurrent anal fistulas were examined, the recurrence rate was the lowest (16%) when the surgical plan was made, considering the MRI findings. The recurrence rate was 57% when MRI findings were not considered and 30% when considered (24). In complex diseases, postoperative recurrence is reduced by 75% with MRI-guided surgery (19). In cases with a clinically simple fistula diagnosed for the first time with a perianal fistula, MRI provides an additional diagnostic contribution of 10% (25).

The most crucial advantage of MRI in fistula evaluation is that it provides images of the sphincter complex equivalent to the planes used in surgery. Distally, the examination should be made up to the lowest end of the fistula. Sometimes the fistula may extend to the proximal thigh. Administration of contrast material may increase the accuracy of the examination. Postcontrast fat-suppressed T1 (T1 FS) images are as successful as T2-weighted images in detecting fistula (26). The distinction between abscess and granulation tissue can only be clearly made with postcontrast images, and contrast-enhanced examination is essential in postoperative cases.Contrast imaging is also useful in differentiating active fistula tracts from treated fibrotic tracts. In fibrotic tracts, there is no fluid signal on T2-weighted images or enhancement in the fistula tract (27).

Abscesses and secondary tracts can complicate fistulas. Secondary extension and abscesses may be in the intersphincteric, ischioanal, and pararectal (supralevator) areas. There may be circular extensions to both sides of the fistula's inner opening. These extensions are called horseshoe fistulas or abscesses. Secondary extensions branching from the primary tract are most common in the ischioanal fossa.

The location of the fistula should be defined in the MRI report. The internal opening, according to the anal clock, should be specified. Extension of the fistula, additional fistula tracts, and abscesses, if any, should be identified. Perianal venous structures can sometimes mimic the fistula. The veins are thin-walled, have a tortuous course, and are generally symmetrical. Hemorrhoids and anal folds may mimic submucosal collections. Hidradenitis suppurativa and sexually transmitted diseases can cause perianal involvement. The absence of a fistula and clinical appearance can easily differentiate it. The pilonidal sinus may extend into the perianal region and form a fistula, but there is no intersphincteric involvement. Intersphincteric involvement is specific for perianal fistula disease and distinguishes it from other inflammatory and infectious diseases of the perianal region (19).

The presence of a perianal abscess in patients with inflammatory bowel disease is a serious issue because it can significantly impact the treatment option. Therefore, MRI has a critical role since it helps determine which patients should receive antibiotics or surgical drainage and which patients require medical immunosuppressive therapy (27).

The limitation of this study is that it was a single-center study, and the contribution of preoperative MRI in patients with perianal abscess was evaluated retrospectively. Multicenter prospective studies can provide clearer criteria for determining which patients should undergo MRI.

CONCLUSION

In conclusion, our study showed that preoperative physical examination, surgical exploration, and preoperative MRI findings in perianal abscesses are valuable in terms of determining the surgical method to be chosen. Also, the number of studies in the literature in which perianal abscesses were evaluated with MRI before emergency surgical treatment is very few, and they are generally not large series studies.

In the present day, through the increasing access and use of technology, MRI, a non-invasive examination, is the optimum imaging method for the preoperative evaluation of the localization of perianal abscess and possible accompanying fistulas. Evaluation with MRI can be useful in preventing complications such as recurrence and incontinence after surgery by visualizing the distant spread of perianal infection, secondary tracts, and abscesses in detail.

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Ethical approval: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study. Study was approved by the Institutional Ethics Committee of University of Health Sciences, Istanbul Prof. Dr. Cemil Taşçıoğlu City Hospital (48670771-514.10).

REFERENCES

- 1. Abcarian H. Anorectal infection: abscess-fistula. Clin Colon Rectal Surg 2011; 24:14.
- Vogel JD, Johnson EK, Morris AM, et al. Clinical Practice Guideline for the Management of Anorectal Abscess, Fistula-in-Ano, and Rectovaginal Fistula. Dis Colon Rectum 2016; 59:1117.
- 3. Parks AG. Pathogenesis and treatment of fistula-in-ano. BMJ 1961; 1: 463-9.
- Zinicola R, Cracco N, Rossi G et al. Acute supralevator abscess: the little we know. Ann R Coll Surg Engl. 2022 Nov;104:645-649. doi: 10.1308/rcsann.2021.0257.
- 5. Mercy Jimenez and Nageswara Mandava. Anorectal Fistula. Treasure Island (FL): Stat Pearls (Internet) Last updated: 09.19.2022.
- Seow-Choen, Phillips RK. Insights gained from the management of problematical anal fistulae at St. Mark's Hospital, 1984-88. Br J Surg 1991; 78: 53941.
- Panes J, Bouhnik Y, Reinisch W, Stoker J, Taylor SA, Baumgart DC, et al. Imaging techniques for assessment of inflammatory bowel disease: joint ECCO and ESGAR evidence-based consensus guidelines. J Crohns Colitis 2013; 7: 556-85.
- 8. Steven V. Turner and Jasvinder Singh. Perirectal Abscess. Treasure Island (FL): Stat Pearls (Internet) Last updated: 08.08.2022.
- Muller LM, Gorter KJ, Hak E, Goudzwaard WL, Schellevis FG, Hoepelman AI, Rutten GE. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin Infect Dis. 2005;41(3):281–288. doi: 10.1086/431587.
- Po-Li Wei JJK, Kuo L-J, Lin H-C. Increased risk of diabetes following perianal abscess: a population-based follow-up study. Int J Colorectal Dis (2013) 28. 2012;235-240(28):235–240.
- Adamo K, Sandblom G, Brannstrom F, Strigard K. Prevalence and recurrence rate of perianal abscess-a population-based study, Sweden 1997-2009. Int J Color Dis. 2016;31(3):669–673. doi: 10.1007/s00384-015-2500-7.

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- Cottam DR, Mattar SG, Barinas-Mitchell E, Eid G, Kuller L, Kelley DE, Schauer PR. The chronic inflammatory hypothesis for the morbidity associated with morbid obesity: implications and effects of weight loss. Obes Surg. 2004;14(5):589–600. doi: 10.1381/096089204323093345.
- Pierpont YN, Dinh TP, Salas RE, Johnson EL, Wright TG, Robson MC, Payne WG. Obesity and surgical wound healing: a current review. ISRN Obes. 2014;2014:638936–638913. doi: 10.1155/2014/638936.
- de Miguel Criado J, del Salto LG, Rivas PF, del Hoyo LF, Velasco LG, de las Vacas MI, et al. MR imaging evaluation of perianal fistulas: spectrum of imaging features. Radiographics 2012; 32: 175-94.
- Carvalho LP, Corleta OC, Mallmann ACM, Koshimizu RT, Spolavori A. Neuropatia pudenda: correlação com dados demográficos, índice de gravidade e parâmetros pressóricos em pacientes com incontinência fecal. Arq Gastroenterol 2002;39(3):139-46.
- Peña A, Hong AR, Midulla P, Levitt M. Reoperative surgery for anorectal anomalies. Semin Pediatr Surg 2003;12(2):118-23.
- Baracho E. Fisioterapia aplicada à obstetrícia, uroginecologia e aspectos de mastologia. 4ª ed. Rio de Janeiro: Guanabara Koogan; 2007.
- Sheikh P, Baakza A. Management of Fistula-in-Ano-The Current Evidence. Indian J Surg. 2014;76:482-486.
- Halligan S, Stoker J. Imaging of fistula in ano. Radiology 2006; 239: 18-33.
- Kuijpers HC, Schulpen T. Fistulography for fistula-in-ano: is it useful? Dis Colon Rectum 1985; 28: 103-4.

- Guillaumin E, Jeffrey RB Jr, Shea WJ, Asling CW, Goldberg HI. Perirectal inflammatory disease: CT findings. Radiology 1986; 161: 153-7.
- Liang C, Lu Y, Zhao B, Du Y, Wang C, Jiang W. Imaging of anal fistulas: comparison of computed tomographic fistulography and magnetic resonance imaging. Korean J Radiol 2014; 15: 712-23.
- 23. Buchanan GN, Halligan S, Bartram CI, Williams AB, Tarroni D, Cohen CR. Clinical examination, endosonography, and MR imaging in preopera-tive assessment of fistula in ano: comparison with outcomebased reference standard. Radiology 2004; 233: 674-81.
- Buchanan G, Halligan S, Williams A, Cohen CR, Tarroni D, Phillips RK, et al. Effect of MRI on clinical outcome of recurrent fistula-in-ano. Lancet 2002; 360: 1661-2.
- Buchanan GN, Halligan S, Williams AB, Cohen CR, Tarroni D, Phillips RK, et al. Magnetic resonance imaging for primary fistula in ano. Br J Surg 2003; 90: 877-81.
- Singh K, Singh N, Thukral C, Singh KP, Bhalla V. Magnetic resonance imaging (MRI) evaluation of perianal fistulae with surgical correlation. J Clin Diagn Res 2014; 8: RC01-4.
- Bartram C, Buchanan G. Imaging anal fistula. Radiol Clin North Am 2003; 41: 443-57.

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