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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Squamous cell skin carcinoma due to chronic sacrococcygeal diseases

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SUMMARY

Introduction/Objective Sacrococcygeal region squamous cell cancers (SCC) due to chronic sacrococcygeal diseases of skin are rare malignancies. The anatomical relation with the anus represents a challenge for diagnosis and surgical treatment. The oncological treatment algorithm is still controversial.
Here, we investigated the clinicopathologic features of skin cancer of the sacrococcygeal region in a total of 10 cases from a surgical oncology reference center.

Methods We retrospectively analyzed the patients who underwent surgery for sacrococcygeal region skin SCC between January 2010 and July 2020.

Results All patients were male, and the mean age was 52.9 ± 10.5 years. In the etiology, five patients had hidradenitis suppurativa, two had human papillomavirus-associated condyloma (Buschke–Lowenstein tumor), and three had pilonidal sinus disease. The mean time between the development of the lesion and malignancy diagnosis was 21.7 ± 5.8 years. In the preoperative evaluation, three patients had bone invasion. None of the patients had anal sphincter or rectal invasion. Also, no patient had lymph node metastasis or distant metastasis. Wide local excision (WLE) was performed in all patients, with three of them with bone resection. Adjuvant chemoradiotherapy was applied to five patients. In 28.5±13.7 months follow-up, local recurrence occurred in five patients and WLE was performed again in these patients. Of these five patients, two eventually became metastatic. Finally, three patients died due to the disease and six patients are still disease free.

Conclusion Sacrococcygeal region SCCs may rarely develop after a long interval from hidradenitis suppurativa, pilonidal sinus disease, and condyloma acuminata. Anal sphincter-sparing WLE can be applied, but sphincter dysfunction may occur. The disease is associated with a high risk of relapse and poor survival.

Keywords: hidradenitis suppurativa; human papillomavirus; pilonidal sinus disease; skin cancer; sacrococcygeal region

INTRODUCTION

Skin cancers of the sacrococcygeal region due to chronic sacrococcygeal diseases are extremely rare and are frequently seen in the fourth–sixth decade of life [1]. Most of the non-melanocytic skin cancers seen in these anatomical regions are squamous cell cancers (SCC), and fewer are basal cell cancers. Chronic wound scars-, hidradenitis suppurativa- (HS), pilonidal sinus disease- (PSD), human papillomavirus- (HPV) related lesions, and giant condyloma acuminata (Buschke–Lowenstein tumor) are known etiological causes [2, 3, 4]. Patients often suffer from chronic sacrococcygeal diseases. Cancer symptoms are not specific; therefore, the diagnosis is often late.

Malignant transformation of the sacrococcygeal chronic diseases is rare, and treatment approaches are controversial [3]. The common characteristic of sacrococcygeal region SCCs is that the high anatomical close relation of anus and sphincter structures represents a challenge for diagnosis and surgical treatment. Most of the presentations in the literature are case reports, and there are no randomized controlled studies. In this study, we aimed to present the characteristics and outcomes of the malignant transformation of benign sacrococcygeal disease to SCC.

METHODS

We retrospectively reviewed 10 patients who underwent surgery due to sacrococcygeal region skin SCC between January 2010 and July 2020.

Patient evaluation

A detailed physical examination was performed for all patients, and routine digital rectal examination and rectosigmoidoscopy were performed. Magnetic resonance imaging (MRI) was preferred to evaluate the tumor's relationship with the anal canal, anal sphincter, and sacrococcygeal bone structures. The diagnosis was made by incisional biopsy in all cases. Endoanal ultrasonography (EUS) was

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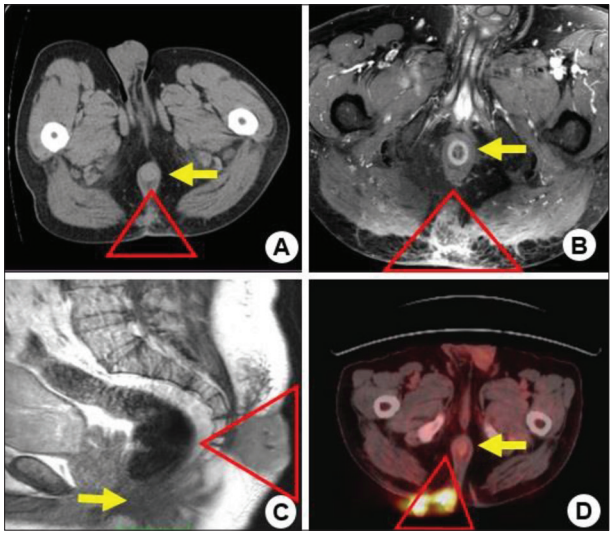

Figure 1. Preoperative radiological images (red triangles show tumors, yellow arrows show anal canal structures); A: preoperative computed tomography image of the tumor in the perianal region; B: preoperative axial MRI image of the perianal tumor; C: preoperative sagittal MRI image of the gluteal tumor; D: preoperative PET-CT image of the tumor located in the gluteal location

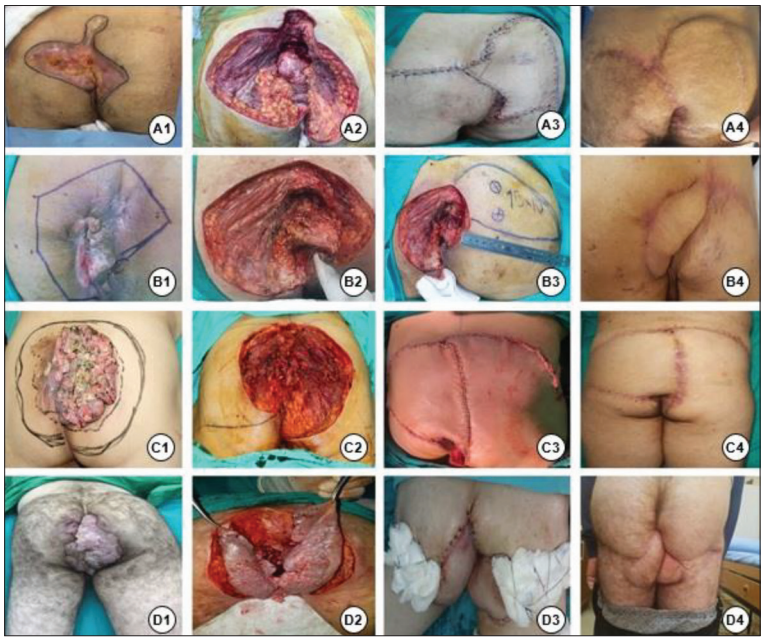

Figure 2. Perioperative images of patients (A, B, C, and D are separate patients); A1, B1, C1, D1: pre-resection tumor appearances; A2, B2, C2, D2: surgical area views; A3, B3, C3, D3: reconstruction procedures; A4, B4, C4, D4: the appearances at long-term follow-up

performed in cases with continued suspicion of sphincter invasion. Thoracoabdominal computed tomography was performed in all the patients to exclude distant metastases. Positron emission tomography / computed tomography (PET-CT) was used when there had been distant and inguinal lymph node metastasis suspicion (Figure 1). Core biopsy was performed from the inguinal lymph node when nodal metastases were suspected. HPV was investigated by a polymerase chain reaction in paraffin-embedded biopsy material taken from all the patients.

Treatment algorithm

In the interdisciplinary tumor board, the patients' individual treatment plans were evaluated, and it was decided to perform wide local excision (WLE) first for all the patients due to non-metastatic disease (Figure 2). A diversion colostomy (loop sigmoidostomy) was performed in cases where tumors were close to the anal canal. Adjuvant chemotherapy (CT) and radiotherapy (RT) were added to cases with surgical margins closer than 1 cm and, if the perineural invasion was identified, in tumors larger than 5 cm.

Data collection

Clinical findings, etiological factors, treatment strategies, histopathological features, and oncological results were examined. Complications were evaluated according to Clavien–Dindo classification (CD) [5, 6]. Recurrences and metastases were determined during the follow-up. Mean survival and disease-free survival times were determined.

Statistical analysis

The data were analyzed using mean, median, minimum, and maximum values. The follow-up time was defined from surgery to death or the last patient contact.

Ethical approval

This study was approved by the Ethics Committee of the University of Cukurova Faculty of Medicine, Adana, Turkey (reference number: 99/11, date: 15.05.2020) and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all the patients for future studies when they were operated on.

RESULTS

Patient characteristics

The clinical characteristics of the patients are given in Table 1. All patients were male, and their mean age was 52.9 ± 10.5 years (range: 39–68 years). In etiology, five patients had HS, two patients had HPV, and three patients had PSD. In six patients, tumors were located at the gluteal region and in four at the perianal margin. One patient had previously undergone surgery for a perianal abscess and one for PSD. The mean time between the development of the lesion and malignancy diagnosis was 21.7 ± 5.8 years. This period was 26.6 ± 2.4 years in HS cases, 15.6 ± 4 years in PSD, and 14.1 ± 2.1 years in HPV. No patient had anal sphincter or rectal invasion; however, three patients had bone invasion. No patient had distant metastasis in the preoperative

Table 1. Our series of 10 cases of HS, HPV, and PSD complicated by SCC

Case	Age (years)	Etiology	Interval (years)	Location	Previous surgery	Bone invasion
1	53	PSD	12	Gluteal	Pilonidal sinus surgery	Yes
2	52	HS	26	PA margin	Abscess drainage	Yes
3	39	HPV	20	PA margin	No	No
4	40	HPV	17	Gluteal	No	No
5	55	HS	25	PA margin	No	Yes
6	68	HS	28	Gluteal	No	No
7	39	HS	30	PA margin	No	No
8	64	HS	24	Gluteal	No	No
9	60	PSD	20	Gluteal	No	No
10	59	PSD	15	Gluteal	No	No

PA – perianal; PSD – pilonidal sinus disease; HS – hidradenitis suppurativa; HPV – human papillomavirus

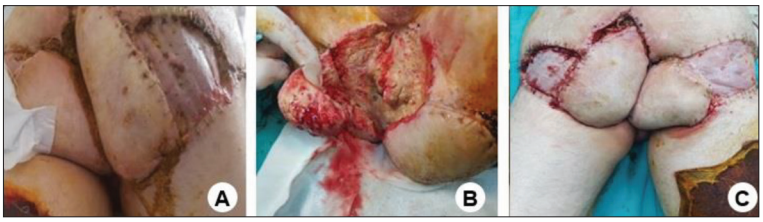

Figure 3. Appearances of flap failure; A: flap failure in the early postoperative period due to fecal contamination; B: flap separation (the patient is in the supine position); C: repeated flap reconstruction after fecal control is achieved

evaluation. Only one patient had inguinal lymph nodes with high SUV-max values on PET-CT. However, it was reactive lymphadenopathy, according to the histopathology examination of the core biopsy.

Treatment

Surgical margins were confirmed with the frozen section, and all of WLE was R0. A diversion colostomy was performed in four patients at the first surgery. Two patients underwent coccygectomy, and one patient had sacrectomy (below S5) with coccygectomy. After resection, the defects that occurred were closed in nine patients by reconstruction performed by plastic and reconstructive surgeon. Only one patient had a CD-3b complication as flap dehiscence requiring reoperation (Figure 3). Postoperative chemo radiotherapy (CRT) was applied to five patients (Table 2). Finally, in three patients, the diversion colostomy never closed and became permanent due to sphincter dysfunction.

Pathological findings

Well-differentiated SCC in eight patients and verrucous SCC (Buschke–Lowenstein

Table 2. Operative and follow-up characteristics of patients

Case	Surgery	Reconstruction	CD	Postoperative CRT	Time of relapse (months) and treatment	Permanent colostomy	Metastasis	Follow-up (months)	Outcome
1	WLE, below S5 sacrectomy, coccygectomy	SAPF	1	No	No	No	No	48	Death
2	WLE, coccygectomy	SAPF	2	CT: 5 FU, cisplatin RT: 4600 cGy TS	13 mo.: WLE, VY FLAP 42 mo.: WLE, below S4 sacrectomy, coccygectomy, colostomy	Yes	Yes (44 mo.)	44	DDD
3	WLE, colostomy	V-Y flap	3b	CT: 5 FU, cisplatin RT: 4800 cGy TS	10 mo.: WLE, RF 14 mo.: WLE, below S4 sacrectomy, coccygectomy	No	No	39	Alive
4	WLE, colostomy	RF	1	CT: 5 FU, mitomycin C RT: 4500 cGy TS, 1440 cGy Bost	8 mo.: WLE, SAPF	No	No	28	Alive
5	WLE, coccygectomy, colostomy	PTF	2	CT: 5 FU, cisplatin RT: 4800 cGy TS	8 mo.: WLE, RF	Yes	No	14	DDD
6	WLE	SAPF	2	No	No	No	No	25	Alive
7	WLE, colostomy	SAPF	2	CT: 5 FU, mitomycin C RT: 3600 cGy TS, 900 cGy PLN	9 mo.: WLE, RF 27 mo.: WLE	Yes	Yes (30 mo)	39	DDD
8	WLE	V-Y flap, RF	1	No	No	No	No	14	Alive
9	WLE	SAPF	1	No	No	No	No	8	Alive
10	WLE	Primer close	1	No	No	No	No	26	Alive

CRT – chemo radiotherapy; CT – chemotherapy; RT – radiotherapy; WLE – wedge local excision; RF – rotation flap; PTF – posterior thigh flap; CD – Clavien–Dindo complication score; SAPF – superior artery perforating flap; DDD – death due to disease; TS – tumor side; PLN – pelvic lymph nodes

Table 3. Histopathological results of patients

Case	Histopathology	Surgical margin (mm)	Perineural invasion	Tumor size (mm)
1	WD SCC	10	No	45 × 27 × 10
2	WD SCC	2	Yes	50 × 35 × 20
3	Verrucous SCC	20	No	100 × 80 × 10
4	Verrucous SCC	8	No	120 × 15 × 10
5	WD SCC	5	No	50 × 40 × 30
6	WD SCC	10	No	45 × 30 × 20
7	WD SCC	15	Yes	70 × 60 × 20
8	WD SCC	10	No	30 × 12 × 10
9	WD SCC	15	No	35 × 32 × 20
10	WD SCC	17	No	35 × 24 × 22

WD – well differentiated; SCC – squamous cell cancers

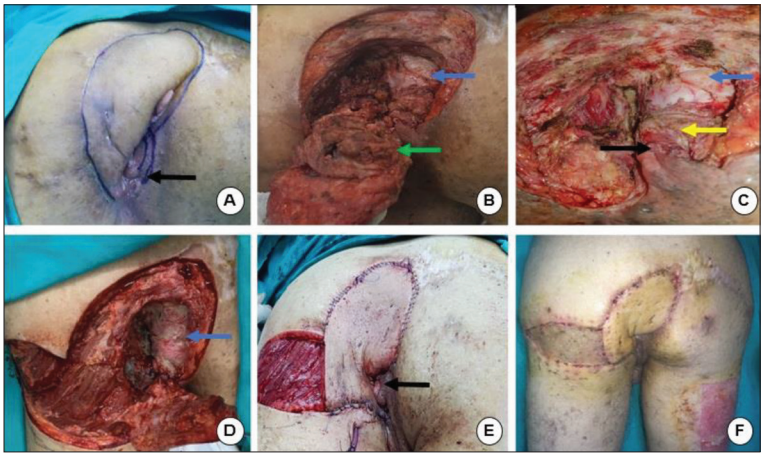

Figure 4. Local recurrence appearances; A: pre-resectional appearances (the black arrows point to the anal verge); B: un-bloc resection with sacrectomy and coccygectomy (the blue arrows point to the distal rectum, and the green arrow points to resected bone); C: surgical area views after resection (the yellow arrow points to the anal sphincter structures); D: rotational flap preparation from the left gluteal area; E: anal verge after reconstruction; F: postoperative appearance

tumor) in two patients were detected. Surgical margin was less than 1 cm in three patients (cases 2, 4, and 5), and perineural invasion was observed in two of the patients (cases 2 and 7). Five patients had tumors larger than 5 cm (cases 2, 3, 4, 5, and 7) (Table 3).

Follow-up

In the follow-up period, local recurrence occurred in five patients. The first relapse occurred within an average of 9.6 ± 2 months. A second WLE was performed on these patients (Figure 4). Local recurrence occurred again in three of these five patients and WLE was performed for the third time. In a mean follow-up of 28.5 ± 13.7 months, four patients died (three due to the disease, one due to myocardial infarction), and six patients are still disease-free (Table 2).

DISCUSSION

In this study, we aimed to present our treatment experiences on skin SCCs that develop from the sacrococcygeal region due to chronic sacrococcygeal diseases, which is rare cancer. The treatment algorithm is not clear in guidelines such as National Comprehensive Cancer Network [7, 8]. Although we are a reference center in surgical oncology and colorectal surgery, we could only present a small number of patients due to the rarity of the disease. However, this study shows that the disease is associated with high recurrence and poor prognosis.

It is known that HS, HPV, and PSD may rarely be an etiologic factor of SCC [2, 3, 4]. Anderson and Dockerty [9] first described malignant degeneration of HS in 1958. The incidence of developing SCC from HS is 1–3.2%. Although HS is more common in women, malignant transformation has been reported more frequently in men [10]. In our series, five patients had HS, and as noted in the literature, all of these patients were male.

Human papillomavirus, another known etiological factor of SCC, is associated with many cancers including head, neck, anal, vulvar, penile, and vaginal carcinomas [11, 12]. The tumor that develops in the perianal region due to HPV is named Buschke–Lowenstein tumor. Clinically, it presents as exophytic, fungal masses with raised morphology. It has benign appearance on histopathology but is locally destructive. It carries a high recurrence rate and a significant potential for malignant transformation [4, 13]. In our series, HPV-associated SCC was detected in two patients.

Another known predisposing disease is PSD and malignant degeneration can occur in approximately 0.1% of patients with untreated PSD [14, 15]. The malignant degeneration process is believed to be similar to pilonidal squamous cell carcinomas and other chronic inflammatory wounds such as burns, osteomyelitis, scars, skin ulcers, and fistulas [2]. Actually, malignant degeneration mechanisms of HS and PSD are still not fully known. It is believed to result from the release of free oxygen radicals by activated inflammatory cells. Genetic damage caused by these radicals is thought to induce neoplastic transformation. In addition, it is claimed that disruption of standard DNA repair mechanisms due to chronic inflammation may play a role in the development of malignancy [16].

The patients with sacrococcygeal SCC usually have chronic perianal or gluteal wounds in their medical history. The cancer symptoms are nonspecific and can be confused with those of the current chronic disease. There may be a long interval between the development of benign illness to cancer. Therefore, the diagnosis is often delayed [17, 18]. According to Kohorst et al. [3], the time from HS to SCC was 28.5 years. In our series, the mean time between the development of the lesion and the diagnosis of malignancy was 21.7 ± 5.8 years, and it was longer in cases with HS than in others.

The treatment strategy of SCC may vary depending on the size of the tumor, the invasion status, and the condition of the complications that may develop (such as fecal incontinence) [18]. Mohs micrographic surgery technique can be used in clinical practice for the treatment of SCC. It is a special form of skin cancer surgery in which the surgeon and pathologist work together. This technique is important in cosmetically (and functionally) sensitive anatomical locations [19]. However, this is not applicable in large and deep invasive tumors such as we have presented in our series.

Abbass and Valente [20] described the treatment algorithm of perianal margin SCC as follows: (i) WLE with 1 cm clear margin should be performed in T1N0 lesions (< 2 cm) without anal sphincter invasion; (ii) T2N0 lesions (2–5 cm) without lymph node involvement can be treated with WLE; however, since the risk of lymph node involvement can be as high as 25%, CRT can be applied; (iii) lymph node-positive patients or T3, T4 patients, should be treated with combined modality CRT as mentioned above, as well as radiotherapy, including the pelvis and bilateral inguinal lymph nodes. In our series, we applied an algorithm similar to that of Abbass and Valente [20] and we applied chemoradiotherapy to tumors larger than 5 cm. In addition, we added adjuvant therapy in cases with perineural invasion. Because perineural invasion is an independent risk factor for lymph node and distant metastases. It has also been associated with lower survival [21]. In our series, the patients with perineural invasion had become metastatic. Also, two-thirds of the patients who died due to the disease in this series had perineural invasion.

According to some authors, routine lymphatic dissection may be more beneficial than CRT for inguinal lymph node metastasis [18]. However, there are no randomized controlled studies on the effect of this on survival. The role of elective lymphatic dissection in high-risk SCC remains undefined with most studies limited to head and neck primary sites. On the other hand, sentinel lymph node (SLN) biopsy is seen as an unproven and yet theoretically appealing surgical technique to accurately stage high-risk SCCs with minimal morbidity, identify the early occult nodal disease, and select patients that might benefit from therapeutic lymphatic dissection or other adjuvant therapy [22]. However, the role of SLN biopsy in these patients remains unclear, as in cases of routine lymphatic dissection. In the present series, only one patient had inguinal lymph nodes with high SUV-max values on imaging. However, it was reactive lymphadenopathy, according to the histopathology of the core biopsy. We think that these lymph nodes are secondary to long-term chronic perianal/gluteal inflammation. Therefore, in the presence of suspected lymph node metastases, core biopsy maybe a guide to avoiding unnecessary routine inguinal dissections.

Sacrococcygeal SCCs can rarely invade the anal sphincter complex [1, 18]. In our series, detailed rectal examination, pelvic MRI, and EUS were used to determine sphincter invasion in cases in which the tumor was close to the anal sphincter complex. In this way, we excluded sphincter or rectal invasion. Although we removed tumors by preserving the anal sphincters and anal canal in all the patients, we would like to state that some open diversion colostomies have become permanent due to the dysfunction of the anal sphincters.

A skin graft may often be required to close the defect after large excision. V-Y flap can often be sufficient. A plastic surgeon's help may be needed to close larger defects [23]. In our series, primary closure was performed in only one patient, reconstruction with flap was required in the others. However, despite loop colostomy, that fecal contamination-related flap failure may develop, as in the third case in our series. Therefore, the option of end colostomy may also be useful in these patients.

In the literature, the local recurrence rate was higher than 50% after SCC resection [24]. Kohorst et al. [3] reported local recurrence in seven of 12 perianal margin SCC cases after WLE. In a total of 4.3 years of follow-up, they lost most of the patients (n = 7) due to the disease. Similarly, the local recurrence rate was high in our series, and three patients died due to cancer, despite receiving CRT. All three of these patients had SCC that developed on the basis of HS. The presence of sinus tracts in HS provides an easy route for malignant cells to spread, and detection of malignant transformation can be difficult against the background of chronic tissue inflammation [25]. The easy spreading or transmission of the malignant cells via sinus tracts may increase the risk of metastasis on HS rather than Buschke–Lowenstein tumor and PSD-based SCC. As seen in the present study, the time between the development of the lesion and malignancy diagnosis is longer in SCCs that develop on the basis of HS. This is an indication of the more insidious course in cases of SCC due to HS. According to the Medline study by Maclean and Coleman [26], the two-year survival rate after SCC diagnosis on the bases of HS was reported to be only 52%. In our series, metastasis and mortality were also seen only in HS cases. In this respect, we can say that HS creates a more aggressive tumor.

Limitations of this study include its retrospective nature and a small number of cases.

CONCLUSION

HS, HPV, and PSD play a role in the development of sacrococcygeal SCC. There may be a long interval between the development of benign illness to cancer. Wide local excision is the most common procedure in treatment. Diversion colostomy and flap reconstruction may be part of surgical treatment. In some cases, CRT may be required, but, unfortunately, there is a high recurrence risk and poor survival despite all treatments.

Conflict of interest: None declared.

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Сквамоцелуларни карцином коже код хроничних болести сакрококцигеалне регије

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САЖЕТАК

Увод/Циљ Сквамоцелуларни карциноми коже су ретки малигни тумори сакрококцигеалне регије. Анатомски однос са анусом представља изазов за дијагнозу и хируршко лечење. Алгоритам онколошког лечења је и даље контроверзан.

У нашем истраживању испитали смо клиничко-патолошке особине карцинома коже сакрококцигеалног региона код укупно десет болесника лечених у референтном центру за хируршку онкологију.

Методе Ретроспективно смо анализирали болеснике који су оперисани због сквамоцелуларног карцинома коже сакрококцигеалне регије у периоду од јануара 2010. до јула 2020. године.

Резултати Сви болесници су били мушког пола, просечне старости 52,9 ± 10,5 година. У етиологији, пет болесника је имало супуративни хидраденитис, двојица су имала кондиломе повезане са хуманим папилома вирусом (тумор Бушке–Левенштајн), а тројица болест пилонидалног синуса. Просечно време између развоја лезије и дијагнозе малигнитета било је 21,7 ± 5,8 година. Ниједан болесник није имао инвазију аналног сфинктера или ректума, али су тројица имала инвазију костију у преоперативној процени. Такође, ниједан болесник није имао метастазе у лимфним чворовима или удаљене метастазе. Широка локална ексцизија извршена је код свих болесника, а код тројице је удружена са ресекцијом костију. Адјувантна хеморадиотерапија примењена је код пет болесника. У праћењу од 28,5 ± 13,7 месеци, локални рецидив се десио код пет болесника и широка локална ексцизија је поново изведена. Од ових пет болесника, два су на крају постала метастатска. Коначно, три болесника су умрла због болести, а шест болесника је и даље без болести.

Закључак Сквамоцелуларни карциноми коже сакрококцигеалне регије могу се ретко развити након дугог интервала присуства супуративног хидраденитиса, болести пилонидалног синуса и кондилома акумината. Може се применити широка ексцизија са презервацијом аналног сфинктера, нажалост са могућом дисфункцијом сфинктера. Болест је повезана са великим ризиком од рецидива и лошим преживљавањем.

Кључне речи: хидраденитис супуратива; хумани папилома вирус; болест пилонидалног синуса; рак коже; сакрококцигеална регија