Original Article / Оригинални рад

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Squamous cell skin carcinoma due to chronic sacrococcygeal diseases

Сквамоцелуларни карцином кожи код хроничних болести сакрококцигеалне регије

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Received: April 5, 2021
Revised: January 17, 2022
Accepted: January 24, 2022
Online First: February 8, 2022
DOI: https://doi.org/10.2298/SARH210405014G

*Accepted papers are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the Serbian Archives of Medicine. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.

Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author’s last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.

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Squamous cell skin carcinoma due to chronic sacrococcygeal diseases

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, 2 had Human papillomavirus associated condyloma (Buschke–Lowenstein tumor), and 3 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; 3 of them with bone resection. Adjuvant chemoradiotherapy was applied to five patients. In a 28.5±13.7 months follow-up, local recurrence occurred in 5 patients, and WLE has performed again in these patients. Of these 5 patients, 2 eventually became metastatic. Finally, 3 patients died due to disease and 6 patients are still free of diseases.

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

Сложилац

Увод/Циљ Сквамоцелуларни карциноми коже су ретки маљтини тумори сакрококцигеалне регије. Анеоматски однос са анусом представља изазов за дијагнозу и хируршко лећење. Алгоритам онколошког лећења је је даље контроверзан. У нашем истраживању испитали смо клиничко-патолошке особине карцинома коже сакрококцигеалног региона код укупно 10 пацијена у периоду од јануара 2010. до јула 2020. године.

Резултати: Сви пацијенти су били мушког пола, просечне старости 52.9±10,5 година. У етиологији, пет пацијена је имало супуративни хидраденитис, три пацијента су имали кондилому (Бушке–Левештајнов тумор), а три пацијента имало пилонидални синус. Просечно време између развоја лезије и дијагнозе малигнитета било је 21,7±5,8 година. Ниједан пацијент није имао инвазију аналног сфингтера или ректума, али су трија имала инвазију костију у пролазници процени. Такође, ниједан пацијент није имао метастазе у лимфним чворовима или удалељене метастазе. Широка локална екцизија извршена је код свих пацијена, а код трија удржана еволуција се дискреционајаости. Адјувантна ЦРТ примена је нека пацијена, а код трија удржана је еволуција се дискреционајаости. Коначно, три пацијента су умрла због болести, а 6 пацијента је и даље бест болести.

Закључак: Сквамоцелуларни карциноми коже сакрококцигеалне регије могу се ређе развији након дугог интервала присуства супуративног хидраденитиса, болести пилонидалног синуса и кондила акумулатиса. Може се применити широка екцизија са претежком аналног сфингтера, нажалост са могућом дисфункцијом сфингтера. Болест је повезана са великим ризиком од рецидива и лошим преживљавањем.

Кључне речи: хидраденитис супуративни; хумани папилома вирус; болест пилонидалног синуса; рак коже; сакрококцигеални регион
INTRODUCTION

Skin cancers of the sacrococcygeal region due to chronic sacrococcygeal diseases are extremely rare and are frequently seen in the 4th-6th decade [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 sacrococcygeal chronic diseases is rare, and treatment approaches are controversial [3]. The sacrococcygeal region SCCs' characteristic 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 ten 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 performed in cases with continued suspicion of sphincter...
invasion. Thoracoabdominal computed tomography was performed in all patients to exclude distant metastases. Positron emission tomography / computed tomography (PET-CT) was used when there is 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 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 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 is identified, and larger than 5 cm tumors.

**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 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 patients for future studies when they operated.

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). In etiology, five patients had HS, two patients had HPV, and three patients had PSD. In 6 patients, tumors were located at the gluteal region and in 4 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 an anal sphincter or rectal invasion; however, three patients had a bone invasion. No patient had distant metastasis in the preoperative 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 9 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 CRT was applied to five patients
(Table 2). Finally, in 3 patients, the diversion colostomy never closed and became permanent due to sphincter dysfunction.

**Pathological findings**

Well-differentiated SCC in 8 patients and verrucous SCC (Buschke-Lowenstein tumor) in 2 patients were detected. Surgical margin was less than 1 cm in 3 patients (cases 2, 4, and 5), and perineural invasion was observed in 2 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 5 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 3 of these 5 patients and WLE has been performed for the third time. In a mean follow-up of 28.5 ± 13.7 months, 4 patients died (3 due to disease, 1 due to myocardial infarction), and 6 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 first described malignant degeneration of HS in 1958 [9]. 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 papilloma virus, 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 as Buschke-Lowenstein tumor. Clinically, it presents as exophytic, fungal masses with a 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 cancers symptoms are nonspecific and confused with those of current chronic disease. There may be a long interval between the development of benign illness to cancer. Therefore, 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 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 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 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 (between 2 and 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 about the effect of this on the survival. The role for 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 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 sentinel lymph node (SLN) biopsy in these patients remains unclear such as routine lymphatic dissection. In the present series, only one patients 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 where 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 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 7 of 12 perianal margin SCC cases after WLE. In a total of 4.3 years of follow-up, they lost most patients (n:7) due to the disease. Similarly, the local recurrence rate was high in our series, and 3 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 in the base of HS was reported as only 52%. In our series, metastasis and mortality were seen in only HS cases too. 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

As a result, 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.
REFERENCES


DOI: https://doi.org/10.2298/SARH210405014G Copyright © Serbian Medical Society

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

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Etiology</th>
<th>Interval (years)</th>
<th>Location</th>
<th>Previous surgery</th>
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<tr>
<td>1</td>
<td>53</td>
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<td>12</td>
<td>gluteal</td>
<td>pilonidal sinus surgery</td>
<td>Yes</td>
</tr>
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<td>2</td>
<td>52</td>
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<td>26</td>
<td>PA margin</td>
<td>apse drainage</td>
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<td>PA margin</td>
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<tr>
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<td>PSD</td>
<td>15</td>
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</tbody>
</table>

PA – perianal; PSD – pilonidal sinus disease; HS – hidradenitis suppurativa; HPV – Human papillomavirus
<table>
<thead>
<tr>
<th>Case</th>
<th>Surgery</th>
<th>Reconstruction</th>
<th>CD</th>
<th>Postoperative CRT</th>
<th>Time of relapse (months) and treatment</th>
<th>Permanent colostomy</th>
<th>Metastasis</th>
<th>Follow-up (months)</th>
<th>Outcome</th>
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<td>SAPF</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>48</td>
<td>death</td>
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<td>SAPF</td>
<td>2</td>
<td>CT: 5 FU, cisplatin RT: 4600 cGy TS</td>
<td>13 mo.: WLE, VY FLAP</td>
<td>Yes</td>
<td>Yes</td>
<td>44 (44 mo.)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42 mo.: WLE, below S4 sacrectomy, coccygectomy, colostomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>WLE, colostomy</td>
<td>V-Y flap</td>
<td>3b</td>
<td>CT: 5 FU, cisplatin RT: 4800 cGy TS</td>
<td>10 mo.: WLE, RF</td>
<td>No</td>
<td>Yes</td>
<td>39</td>
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<tr>
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<td>WLE, colostomy</td>
<td>RF</td>
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<td>CT: 5 Fu, mitomycin C RT: 4500 cGy TS, 1440 cGy Bost</td>
<td>8 mo.: WLE, SAPF</td>
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<td>No</td>
<td>28</td>
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<td>PTF</td>
<td>2</td>
<td>CT: 5 FU, cisplatin RT: 4800 cGy TS</td>
<td>8 mo.: WLE, RF</td>
<td>Yes</td>
<td>No</td>
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<td>DDD</td>
</tr>
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<td>No</td>
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<td>7</td>
<td>WLE, colostomy</td>
<td>SAPF</td>
<td>2</td>
<td>CT: 5Fu, mitomycin C RT: 3600 cGy TS, 900 cGy PLN</td>
<td>9 mo.: WLE, RF 27 mo.: WLE</td>
<td>Yes</td>
<td>Yes</td>
<td>39 (30 mo)</td>
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<td>V-Y flap, RF</td>
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<td>No</td>
<td>No</td>
<td>26</td>
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</table>

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

<table>
<thead>
<tr>
<th>Case</th>
<th>Histopathology</th>
<th>Surgical margin (mm)</th>
<th>Perineural invasion</th>
<th>Tumor size (mm)</th>
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<tbody>
<tr>
<td>1</td>
<td>WD SCC</td>
<td>10</td>
<td>No</td>
<td>45 × 27 × 10</td>
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<td>2</td>
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<tr>
<td>3</td>
<td>Verrucous SCC</td>
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WD – well differentiated; SCC – squamous cell cancers
**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
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.
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