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Pilonidal sinus disease carcinoma: Survival and recurrence analysis

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Abstract

Background: The study aims to determine the survival and recurrence rates of pilonidal sinus disease (PSD) carcinoma.

Methods: The data were collected retrospectively by searching the worldwide literature for all reports of carcinoma developing on the background of PSD. The results were presented using Kaplan–Meier curves.

Results: Between 1900 and 2022, 140 cases of PSD carcinoma were published in 103 papers, with follow-up data available in 111 cases. Squamous cell carcinoma constituted 94.6% of the cases ($n = 105$). The disease-specific survival rate was 61.7% for 3 years, 59.8% for 5 years, and 53.2% for 10 years. There was a significant survival difference between stages: 80.0% in stages I and II, 70.8% in stage III, and 47.8% in stage IV ($p = 0.01$). The 5-year survival in G1-tumors was better than G2 and G3-tumors at 70.5% and 32.0%, respectively ($p = 0.002$). Recurrence occurred in 46.6% of the patients. The time-to-recurrence in patients treated with curative intention averaged 15.1 months (1–132 months). Local, regional, and distant recurrence was observed in 75.6%, 33.3%, and 28.9% of the recurrent tumors, respectively.

Conclusions: Pilonidal sinus carcinoma has a worse prognosis than primary cutaneous squamous cell carcinoma. Poor prognostic factors include advanced-stage disease and poor differentiation.

KEYWORDS

infection degeneration, Marjolin's ulcer, pilonidal sinus carcinoma, pilonidal sinus disease, squamous cell carcinoma, survival analysis

1 | INTRODUCTION

Pilonidal sinus disease (PSD) is a common pathology in surgical practice. Chronic and neglected cases can show malignant degeneration, which is a rare complication seen in approximately 0.1% of patients.[1] The disease is documented in case reports and small case series with a total of about 140 cases published in the literature so far.[2]

Squamous cell carcinoma (SCC) is the most common histological type of pilonidal sinus disease carcinoma (PSDCA), followed by basal cell carcinoma and mixed-type carcinoma.[3] Various authors reported a 5-year survival rate of about 55%–61%, which is far worse than primary cutaneous squamous cell carcinoma (cSCC).[4,5]

Until now, there has been a lack of comprehensive analyses of survival data in the medical literature. It seems that there is a gap in

the knowledge regarding the survival of specific subgroups such as poorly differentiated carcinomas and patients who receive adjuvant therapy. In this paper, we present a survival analysis of all published cases of PSDCA, aiming to provide more insights into the behavior and prognosis of the disease.

2 | MATERIALS AND METHODS

To find all reported cases of PSDCA, we searched the available literature in the online medical databases (PubMed, ScienceDirect, Scopus, Medline, Web of Science, Cochrane, and Google Scholar) using the following combinations of keywords: "pilonidal AND sinus AND carcinoma; pilonidal AND carcinoma; pilonidal AND cancer; pilonidal AND tumor; pilonidal AND squamous". The context and reference list of each article were analyzed to detect any further papers that are not available in the online databases.

Inclusion criteria included all case reports and case series that described patients with carcinoma developing secondary to PSD. Exclusion criteria included carcinomas developing in the pilonidal areas without any evidence of prior pilonidal disease (primary skin neoplasms). Reports with no follow-up data were not included in the final analysis.

The data were extracted from the reports and organized using Microsoft Excel (Microsoft® Excel 2019, Version 16.0.11901.20170). The collected data sets about each case included the demographics (age and gender), the histological characteristics (type, grade), the stage of the tumor (tumor size, local invasion, regional or distant metastases), the application of adjuvant therapy, the results (cure, recurrence with time and location, death with the timepoint and cause), and the follow-up period.

For survival analysis, Kaplan–Meier curves were generated using GraphPad-Prism (GraphPad Software, LLC ® 2021; Version 9.3.1 [471]). *p* Values were calculated using the same software for subgroup comparisons. Due to the small sample size, the calculation of statistical significance was based on the log-rank Mantel–Cox test. The literature-based study was exempted from the requirement of ethical approval by the ethical commission of the Medical Association of Lower Saxony.

3 | RESULTS

The literature research yielded a total of 140 eligible cases of pilonidal sinus carcinoma, which were published between 1900 and 2022 in 103 papers worldwide. After excluding 29 cases with no follow-up data, the final analysis included 111 cases (Figure 1).

3.1 | Study cohort

The age of the patients ranged from 19 to 86 years (mean ± standard deviation [SD]: 54.0 ± 11.5 years; median 56.0 years). Only 9% (*n* = 10/111) of the patients were females. SCC constituted 94.6% of the cases (*n* = 105/111). The grade of the tumor was not available in 51.4% of cases (*n* = 57/111). In 64.8% (*n* = 35/54), 29.6% (*n* = 16/54), and 5.6% (*n* = 3/54) of the cases with a known grade, the tumor was well differentiated, moderately differentiated, and poorly differentiated, respectively.

The tumor, nodes, metastases (TNM) stage was determined based on the Union for International Cancer Control (UICC) staging system for cutaneous SCC.[6] In 13.5% of the cases (15/111), the stage could not be determined due to missed data. Since PSDCA is a midline process in most cases, contralateral lymph node involvement was considered similar to ipsilateral involvement (rather than distant metastases as described in the UICC staging system). The tumor was in stages I, II, III, and IV in 3.1% (*n* = 3/96), 5.2% (*n* = 5/96), 47.9% (*n* = 46/96), and 43.8% (*n* = 42/96) of cases, respectively.

As Figure 1 shows, 9.0% of the patients (*n* = 10/111) received palliative therapy only due to surgery refusal, reduced general condition, or advanced disease at presentation. The remaining patients (91.0%, *n* = 101/111) were treated with curative intention, whereby adjuvant therapy (radiotherapy, chemotherapy, or both) was applied after surgery in 29.7% (*n* = 30/101) of these patients.

The follow-up period varied considerably from 1 month to 18 years with an average of 3.4 years (mean ± SD: 40.6 ± 45.3 months; median 24.0 months). Locoregional recurrence was managed with radical treatment when feasible and a cure was achieved in 20 of the 47 patients with recurrence (42.6%). A total of eight patients (7.2%, *n* = 8/111) died from other causes during the follow-up period.

3.2 | Survival analysis

Figure 2 shows the analysis of disease-specific survival using Kaplan-Meier survival curves. The overall, disease-specific survival rate equaled 61.7% for 3 years, 59.8% for 5 years, and 53.2% for 10 years (Figure 2A). No disease-specific mortalities were documented after 81 months (6.75 years).

There was no significant gender-specific difference in survival. As shown in Figure 2B, the 5-year survival seemed to be slightly better in women (76.2%) than in men (58.2%). However, no statistical difference was observed (*p* = 0.32), perhaps due to the difference in the sample size and the smaller female cohort (a total of 10 women vs. 101 men).

The 96 patients with available TNM-stage (86.5% of all 111 patients) were stratified into three groups: stages I and II (8.3%, *n* = 8/96), stage III (47.9%, *n* = 46/96), and stage IV (43.8%, *n* = 42/96). Due to the small sample size, further stratification for each stage was not possible. Figure 2C compares the results between the three groups and shows a 5-year survival of 80.0% in the early-stage disease versus 70.8% in stage III and 47.8% in stage IV. These differences were statistically significant (*p* = 0.01). Long-term survival for stage IV disease equaled 35.9%.

The histological tumor grade was available in 48.6% (*n* = 54/111) of the patients. For survival analysis, the study cohort was stratified

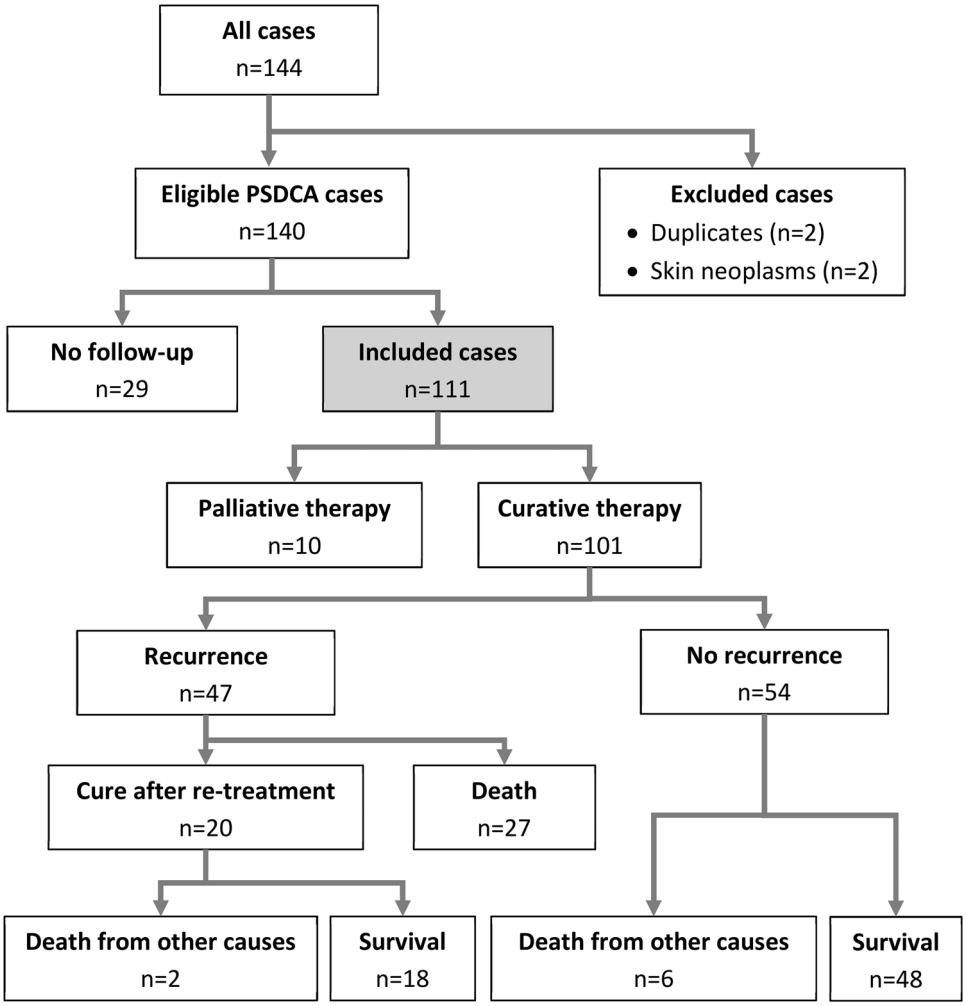

FIGURE 1 Flow diagram of the included and excluded pilonidal sinus carcinoma (PSDCA) cases in the study.

into two groups: G1 tumors (n = 35/54) in the first group and both G2 (n = 16/54) and G3 (n = 3/54) tumors in the second group. Figure 2D shows a significant difference between these two groups with a 5-year survival of 70.5% in the well-differentiated tumors versus 32.0% in the remainder (p = 0.002).

3.3 | Recurrence analysis

Recurrence occurred in 46.6% (n = 47/101) of the patients who were treated with curative intent. The time-to-recurrence was reported in only 40 of the 47 recurrence cases (85.1%) and averaged about 15 months (mean ± SD: 15.1 ± 24.8 months; median 8.0 months). The time to first recurrence extended from one month after a reported R0-resection[7] to 132 months in a patient with multiple recurrences of the pilonidal disease with re-confirmation of malignancy after 11 years.[8]

The site of recurrence was explicitly reported in 45 out of the 47 patients who had recurrence after curative treatment. Local, regional, and distant recurrence were observed in 75.6% (n = 34/45), 33.3% (n = 15/45), and 28.9% (n = 13/45) of the recurrent tumors, respectively. Since many patients exhibited simultaneous recurrence in multiple locations, one patient may be included in two or three of these groups at the same time, which explains the overlap. For distant metastases, palliative chemotherapy and/or radiotherapy were offered. For resectable recurrent tumors, a repeat radical surgery was performed. As Figure 1 shows, this was successful in 42.6% of the patients with recurrence (n = 20/47).

3.4 | Adjuvant therapy

Further analysis included the patients who received adjuvant therapy (radiotherapy, chemotherapy, or both) for curative intention after the exclusion of the 10 patients with primary palliative therapy. As shown in Figure 3A, the 5-year recurrence-free survival equaled 54.4% in patients who received adjuvant therapy (n = 28) versus 52.9% in those without adjuvant therapy (n = 63); no significant difference was observed (p = 0.73). The 5-year survival in the group of adjuvant therapy was at 43.9% worse than that without adjuvant therapy at

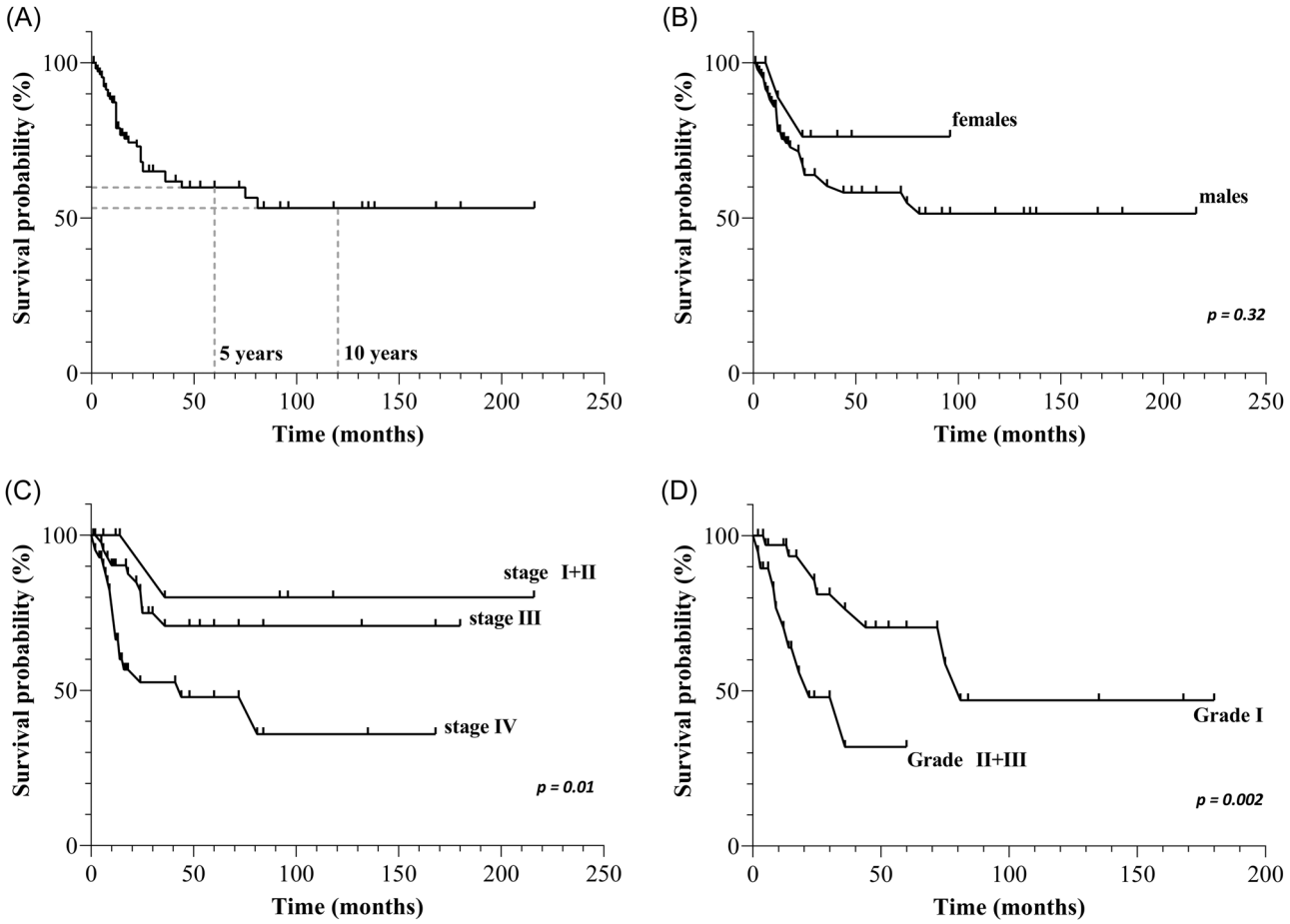

FIGURE 2 Survival analysis using Kaplan–Meier curves. (A) Disease-specific survival of all patients ($n = 111$). (B) Gender-specific survival of all patients ($n = 111$). (C) Stage-specific survival of patients with a known TNM stage ($n = 96$). (D) Grade-specific survival of patients with a known histological grade ($n = 54$).

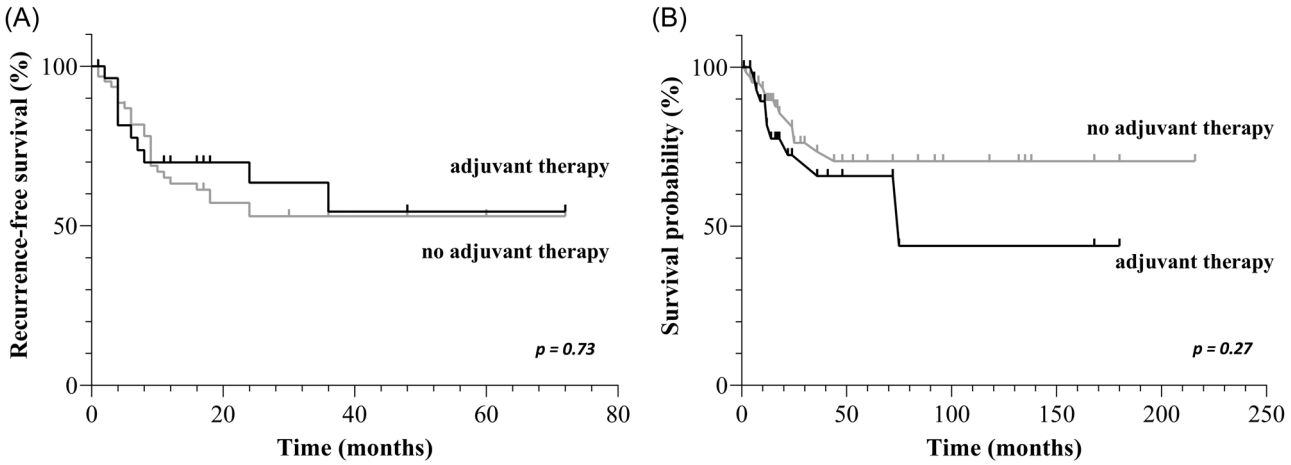

FIGURE 3 Survival analysis of the patients who received adjuvant radiotherapy and/or chemotherapy (black) compared with those who did not receive adjuvant therapy (gray). (A) Recurrence-free survival. (B) Disease-specific survival.

70.4%, albeit with no statistical significance ($p = 0.27$) (Figure 3B). The worse survival rate with adjuvant treatment can be attributed to the already advanced stage or other poor prognostic factors.

4 | DISCUSSION

The first PSDCA case was reported in 1900 by Dr. Heinrich Wolff from Germany, in which a SCC was detected after the second recurrence of a PSD.[9] Since then, sporadic publications in different languages reported PSDCA cases from many countries around the world. It was clear to many authors that the disease shows a more aggressive course and a worse prognosis than primary cutaneous SCC, but it was not possible to determine the exact survival rates, since no single center was able to collect the needed number of cases to perform the needed analysis.

This comprehensive literature research included all published PSDCA cases with the identification of 111 reports that include follow-up data. The survival analysis showed an overall 5-year survival of 59.8%. This coincides with Wronski's estimations in 2019, who reported an overall 5-year survival rate between 55% and 61%.[10] As expected, the subgroup analysis showed a poor survival of 47.8% in stage IV disease and 32.0% in moderately and poorly differentiated tumors.

Although the locally or systemically advanced disease is already considered a poor prognostic factor in PSDCA,[7,11] the results regarding tumor grade were sometimes biased because of the small sample size. Some authors found no association between tumor differentiation and survival, calling this an "unexpected finding."[12] In our study, long-term survival in the G1-group (47.0%, analysis of the only 54 patients with available grade data) was less than the overall 5-year survival (53.6%, analysis of all 111 patients). To explain this finding, we think that the majority of the cases with unavailable data was well-differentiated, which would compensate for this difference.

The same poor prognostic factors were identified in cSCC. In their multivariate analysis, Schmults et al. found that a more advanced stage (greater extent or deep invasion of fat), positive lymph nodes, or poor differentiation of cSCC was associated with higher mortality.[13] Nevertheless, the overall prognosis of PSDCA was significantly worse than cSCC (Table 1). Even in early stages or well-differentiated PSDCA, the 5-year survival rate stays at about 70% compared with 95% in cutaneous SCC.[13] Unlike cSCC, which is often described as an "easily curable" tumor, PSDCA is considered a different entity that behaves more aggressively.[5]

Marjolin's ulcer was described as early as 1951 in chronic wounds accompanying osteomyelitis. These "secondary" SCCs progress rapidly, infiltrate extensively, and spread widely; they were thus labeled as very malignant tumors with a poor prognosis.[17] Table 1 shows that PSDCA is not very different from Marjolin's ulcer carcinoma, with roughly similar recurrence and survival rates.[15]

Multiple mechanisms may explain the aggressive behavior of PSDCA compared with cSCC. Complete excision of locally advanced tumors that are associated with deep infiltration of soft tissues or bone may be difficult or not feasible.[12] The chronic infection and inflammatory reaction accompanied by local scarring and fibrosis may compromise the local defense mechanisms, which limits the efficiency of the immune system to recognize the tumor cells as "not self," thus promoting tumor progression.[18]

Further particular anatomical and mechanical factors may also contribute to the ability of these tumors to disseminate. The preformed fistula tracts, where carcinogenesis occurs, may serve as a pathway for local and systemic metastases.[11,19] The continuous shear forces through local pressure and friction in the sacral and gluteal region during walking can drive the tumor cells to leave their site of origin and disseminate more quickly, the same concept that underlies the principle of "no-touch technique" in oncologic surgery.[20]

Surprisingly, our study showed no benefit of adjuvant treatment in PSDCA. As early as 1969, Boutet suggested that these tumors show only moderate sensitivity to radiation.[21] Sagi et al. also suggested many years afterward that radiation and chemotherapy are unlikely to affect prognosis.[22] The survival analysis performed in this study can support these statements. This underlines the importance of surgical treatment as the single best chance of cure in PSDCA, with adjuvant radiochemotherapy being considered in patients with poor prognostic factors or for palliative purposes.[10] Neoadjuvant therapy may improve the resectability of locally-advanced tumors and potentially reduce local recurrence,[23] although no concrete data are available.

TABLE 1 A comparison of survival and recurrence rates between pilonidal sinus carcinoma and other skin neoplasms.

	cSCC[13,14]	MU[15,16]	PSDCA
Regional metastases at diagnosis	3.7%	20%–66%	8.5%
Distant metastases at diagnosis	0.2%	20%–40%	5.4%
Recurrence rate after curative resection	4.6%	20%–50%	46.6%
3-year survival rate	95.3%	65%–75%	61.7%
5-year survival rate	93.6%	40%–69%	59.8%
10-year survival rate	93.6%	34%	53.2%

Abbreviations: cSCC, cutaneous squamous cell carcinoma; MU, Marjolin's ulcer; PSDCA, pilonidal sinus carcinoma.

4.1 | Limitations

The study suffers from some limitations that may weaken or bias the results. Due to the rarity of the disease and paucity of reports, only a relatively small number of cases was involved, especially in the subgroup analyses. Furthermore, the data were extracted retrospectively from the literature and not from a cancer registry. Standard reporting as well as many data sets were missing, which further contributed to the small subgroup size.

The included cases were reported over more than a century. Therefore, the overall analysis may not reflect the current developments in diagnosis and therapy. Additionally, including cases from different countries and institutions worldwide with variations in therapy protocols can alter the results. Histological variations would also play a role. For example, seven SCC cases were classified under the verrucous subtype, which usually shows a more favorable prognosis.[24] Finally, some follow-up data were deficient. As Figure 1 shows, follow-up data were missing in 29 published cases and the mean follow-up period was only 3.4 years, although some patients could be followed for 18 years. This would limit the detection of late recurrence and mortality.

5 | CONCLUSIONS

In this study, we tried to provide new insights about the overall and subgroup survival of pilonidal sinus carcinoma as well as the recurrence rates after curative treatment. The analysis showed that the prognosis of the disease is considerably worse than cSCC with higher recurrence rates. The best prognosis is seen with early-stage disease and well-differentiated tumors, which stresses the importance of early detection and treatment. It seems that adjuvant therapy does not have additional value in PSDCA compared with surgery alone.

Due to the rarity of the disease and the mentioned study limitations, especially the missing data and the short follow-up periods, it is difficult to draw definite conclusions about the results. It is important to report and document all PSDCA cases in national cancer registries, especially in countries with a high incidence of pilonidal disease.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. A complete list of publications that were included in this analysis can be found online in the Supporting Information section at the end of this article. The full data sets that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was exempted from the requirement of ethical approval by the ethical commission of the Medical Association of Lower Saxony. The analysis done in this study did not contain any interventions that could potentially cause harm to human participants, as it solely analyses anonymized statistical data from the literature. It neither contains nor discloses any patient-related information.

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