Oncology and Translational Medicine
DOI 10.1007/s10330-020-0400-0
February 2020, Vol. 6, No. 1, P1–P9

ORIGINAL ARTICLE

# Clinical characteristics and survival outcomes of perianal Paget's disease: A SEER population-based study*

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## Abstract

**Objective** The aim of the study was to analyze the clinical features of patients with perianal Paget's disease (PPD) and investigate prognosis risk factors.

**Methods** The SEER*Stat software was used to identify 116 PPD patients from 1975 to 2015 in the SEER research database. The Kaplan-Meier method was used to conduct a univariate analysis for PPD patients. The differences in survival rates were evaluated using the log-rank test. The differences in the clinicopathological features of PPD patients with or without anorectal carcinoma were compared using the chi-square test.

**Results** The median survival time of PPD patients was 44 months. The median age of onset was 73 years old. The 43.10% of the patients were alive at the end of follow up, and only 12.93% of the patients died of PPD. Elderly (age > 70 years; $\chi^2$ = 9.453, $P$ = 0.002), poor differentiation ($\chi^2$ = 46.557, $P$ = 0.000) and abdominal perineal resection (APR; $\chi^2$ = 46.557, $P$ = 0.000) were unfavorable risk factors of prognosis. Nearly 50% of PPD had combined with other malignancies, and over 22.41% of those had multiple primary neoplasms (3 or more). PPDs predisposed concurrent malignancy, and 48.21% of PPD patients with other malignancies combined with anorectal carcinoma in the study. Stage ($\chi^2$ = 10.127, $P$ = 0.018), and surgical method ($\chi^2$ = 12.245, $P$ = 0.007) were statistically significant in the PPD patients with or without anorectal carcinoma. The 16.07% of patients had multiple lesions of Paget's.

**Conclusion** Patients with PPD have a favorable survival, while the disease-specific mortality is low. Diagnosed age, differentiation, and surgical methods were the influence factors of prognosis in PPD patients. PPDs with anorectal carcinoma is of most important in further investigation.

Received: 7 January 2020
Revised: 1 February 2020
Accepted: 20 February 2020

**Key words:** perianal Paget's disease (PPD); extramammary Paget's disease; SEER database; survival analysis

Paget's disease (PD), first described by Sir James Paget in 1874 [1], was initially found in the breast. Two decades later, in 1889, Crocker reported extramammary Paget's disease (EMPD) of a genital site [2]. In 1893, perianal Paget's disease (PPD) was discovered [3]. Since then, less than 200 cases have been mentioned in the literature. Due to its rarity, and frequent association with concurrent malignancies, its management remains challenging. Wietfeldt [4] summarized a number of PPD cases and established a treatment guideline for different situations. However, these cases were mostly from papers with small sample sizes, which inevitably results in selective bias. Up to now, the largest study [5] came from the Memorial Sloan-Kettering Cancer Center, which involved 65 patients over a 6 year follow-up period. Other than that, most papers have been case series. Several papers have focused on EMPD using the SEER database. Initially, Karam and Dorigo [6] asserted that the

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* Supported by grants from the Scientific Research Staring Foundation for the Returned Overseas Scholars and the Scientific Research Foundation of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (No. 2019A16).

disease-specific survival of invasive EMPD is generally favorable. Later, they identified that patients had a long-term increased risk of developing secondary malignancies of invasive EMPD and suggested a prolonged follow-up period [7]. Yao *et al* [8] found that vaginal lesions, older age, concurrent malignancy, distant metastasis, and being male are risk factors of EMPD survival and that surgery is a protective factor. However, EMPD is a group of diseases that encompasses multiple lesion sites, including the peri-anus.

As far as we know, this is the first paper that focusses on PPD using the SEER database and is one of the largest population-based studies about PPD. Although the study was retrospectively conducted, we believe that the large sample size will help to improve our understanding of this rare onset disease and offer interesting insights that can be used in clinical practice and surgical management.

## Materials and methods

### Data source

The SEER database is one of the world's largest open cancer databases. Representing almost 30% of the population of the United States of America, the database contains data on cancer incidence and mortality from 18 population-based registries. We signed the SEER research data agreement to access the SEER database. The SEER database and SEER-stat software (SEER*Stat 8.3.5) were used to search for PPD patients between 1975 and 2015 with a known age (≥ 18 years). Year of diagnosis, sex, race, primary site, differentiation grade, stage, histological type, surgery, cause of death, total number of *in situ*/malignant tumors, reason for no cancer-directed surgery, radiation, chemotherapy, number of PPD(s), and sequence at diagnosis were extracted from the SEER database.

### Statistical analysis

Baseline patient demographic characteristics and tumor information were compared using the Pearson's chi-square test for categorical variables. Overall survival (OS) was measured from the date on which the first definite diagnosis was made until the date of death, the date last known to be alive, or to 2015. Disease-specific survival (DSS) was measured from the date of diagnosis to the date of deaths, which were associated with PPD. Survival curves were generated according to the Kaplan-Meier method and compared using the log-rank test in a univariate analysis. All the statistical analyses were performed using SPSS statistical software, version 25.0 (IBM Corp, Armonk, NY). All *P*-values were two-sided. A *P*-value of < 0.05 was considered statistically significant.

## Results

### Characteristics of all the PPD patients included in this study

A total of 116 patients diagnosed with PPD in the SEER database from 1975 to 2015 were included in this study. The median follow-up time was 45.5 months, with the longest follow-up time being 340 months. The 63.79% of the patients were > 70 years old, and 50.0% of the patients were males. The 84.48% of the patients were white, while 2.59% were black. The anus was the most common primary site, affecting 56.90% of the patients, followed by the anal canal at 31.03%, and the overlap rectum at 12.07%. Localized PPD covered 42.24%. 49.14% of the patients had one *in situ*/malignant tumors, while 28.45% and 22.41 % of the patients had two and more than two *in situ*/malignant tumors, respectively. The 69.83% of the patients underwent a surgical resection, followed by excisional biopsy, local tumor excision, and abdominal perineal resection (APR) in 56.79% and 16.05% of the patients, respectively. Surgery was not recommended in 77.14% of the patients who did not undergo surgery. The 43.10% of the patients were alive at the end of follow up, and only 12.93% of the patients died of PD. The characteristics of the patients with PPD are shown in Table 1.

### Prognosis analysis of the PPD patients

The median survival time of the 116 patients diagnosed with PPD was 44 months. The 1-year survival rate was 70.69%, while the 3-year, 5-year, 10-year, and 15-year survival rates were 48.28%, 31.03%, 10.34%, and 3.45%, respectively. The overall survival curve and disease-specific survival curve are shown in Fig. 1. The univariate survival analysis of the clinical and pathological factors indicated that age at diagnosis ($\chi^2$ = 9.453, $P$ = 0.002, optimal cutoff value was 70 years old), grade of differentiation ($\chi^2$ = 46.557, $P$ = 0.000), and surgical method ($\chi^2$ = 4.790, $P$ = 0.029) had a significant influence on the survival of patients with PPD (Fig. 2). Sex, race, primary site, stage, and other factors were not significantly related to prognosis (Table 2).

### Characteristics of the PPD patients with anorectal carcinoma

In the selected database, 27 patients were diagnosed with PPD and anorectal carcinoma. The median follow-up time in these patients was 39 months, the longest follow-up time was 199 months, and the shortest follow-up time was 2 months. The 62.96% of the patients were > 70 years old, and 59.26% of the patients were male. The 81.48% of the patients were white, while 3.70% were black people. The anus was the most common primary site, affecting 59.26% of the patients, followed by the

**Table 1** Characters of perianal Paget's disease patients included in this study

| Clinical characteristics | Number | Percentage (%) |
|---|---|---|
| Total number | 116 | 100.00 |
| Age at diagnosis (years) | | |
| ≤ 70 | 42 | 36.21 |
| > 70 | 74 | 63.79 |
| Sex | | |
| Male | 58 | 50.00 |
| Female | 58 | 50.00 |
| Race | | |
| White | 98 | 84.48 |
| Black | 3 | 2.59 |
| Other | 15 | 12.93 |
| Primary site | | |
| Anus | 66 | 56.90 |
| Anal canal | 36 | 31.03 |
| Overlap rectum | 14 | 12.07 |
| Stage | | |
| Localized | 49 | 42.24 |
| Regional | 21 | 18.10 |
| Distant | 5 | 4.31 |
| Unknown | 41 | 35.34 |
| Total number of *in situ*/malignant tumors for patient | | |
| 1 | 60 | 51.72 |
| 2 | 30 | 25.86 |
| ≥ 3 | 26 | 22.41 |
| Surgery | | |
| Yes | 81 | 69.83 |
| No | 35 | 30.17 |
| Surgical method | | |
| Excisional biopsy, local tumor excision | 46 | 56.79 |
| APR | 13 | 16.05 |
| Polypectomy | 1 | 1.23 |
| Others | 21 | 25.93 |
| Reason of no cancer-directed surgery | | |
| Not recommend | 27 | 77.14 |
| Recommend, but not performed | 8 | 22.86 |
| Survival status | | |
| Alive | 50 | 43.10 |
| Paget's disease | 15 | 12.93 |
| Others (not by Paget's disease) | 51 | 43.97 |
| Cause of death | | |
| Rectum and rectosigmoid junction malignancy | 20 | 30.30 |
| Colon malignancy | 5 | 7.58 |
| Other malignancy (anus, breast, lung, bronchus, non-melanoma skin malignancy or Hodgkin lymphoma) | 14 | 21.21 |
| Cardio-cerebrovascular disease | 12 | 18.18 |
| Urogenital diseases (urinary bladder, vulva, or prostate disease) | 3 | 4.55 |
| Septicemia | 3 | 4.55 |
| Chronic liver disease | 1 | 1.52 |
| Other causes | 8 | 12.12 |

anal canal at 18.52% and overlap rectum at 22.22%. The 40.74% of the patients had one *in situ*/malignant tumor, while 25.93% and 33.33 % of the patients had two and more than two *in situ*/malignant tumors, respectively. About 74.07% of the patients were synchronous, while only 18.52% were metachronous. The 77.78% of the patients underwent surgery, followed by excisional biopsy, local tumor excision, and APR in 76.19% and 19.05% of the patients, respectively. The 83.33% of those that did not undergo surgery was because it was not recommended. The 77.78% of the patients did not undergo radiation or cancer-directed radiation, while 33.33% of the patients received chemotherapy. The 40.74% of the patients were alive at the end of follow up, and only 14.81% of the patients died of PD. Characters of the patients with PPD and anorectal carcinoma are shown in Table 3.

## Analysis of the influencing factors on PPD patients with anorectal carcinoma

The stage ($\chi^2 = 10.127$, $P = 0.018$), and surgical method ($\chi^2 = 12.245$, $P = 0.007$) were statistically significant in the PPD patients with or without anorectal carcinomas. Age at diagnosis, sex, race, cause of death, number of tumors, the total number of benign/borderline tumors, the total number of *in situ*/malignant tumors, and reason for not undergoing cancer-directed surgery was not statistically significant between PPD patients with or without anorectal carcinomas (Table 4).

## Characteristics of PPD patients with other malignant tumors

In the study, a total of 56 patients diagnosed with PPD and other malignant tumors in the SEER database from 1975 to 2015 were included. The median follow-up time was 70 months, the longest follow-up time was 340 months, and the shortest follow-up time was 2 months. The 48.21% of the patients were > 70 years old, and 55.36% of the patients were male. The 83.93% of the patients were white, while 5.36% were black. The 55.36% of the patients had two *in situ*/malignant tumors, while 32.14%, 10.71%, and 1.79% of the patients had 3, 4, and 5 *in situ*/malignant tumors, respectively. The 83.93% of the patients had one PPD, while 14.29% and 1.79% of the patients had 2 and 4 PPDs, respectively. PPD and the other malignant tumors were diagnosed at the same time in 53.57% of the patients, while only PPD was initially diagnosed in 14.29% of the patients. The 35.71% of the patients were alive at the end of the follow-up period. Only 17.86% of the patients died of PD, while 46.43% of the patients died from other causes. Characteristics of the patients with PPD and other malignant tumors are shown in Table 5.

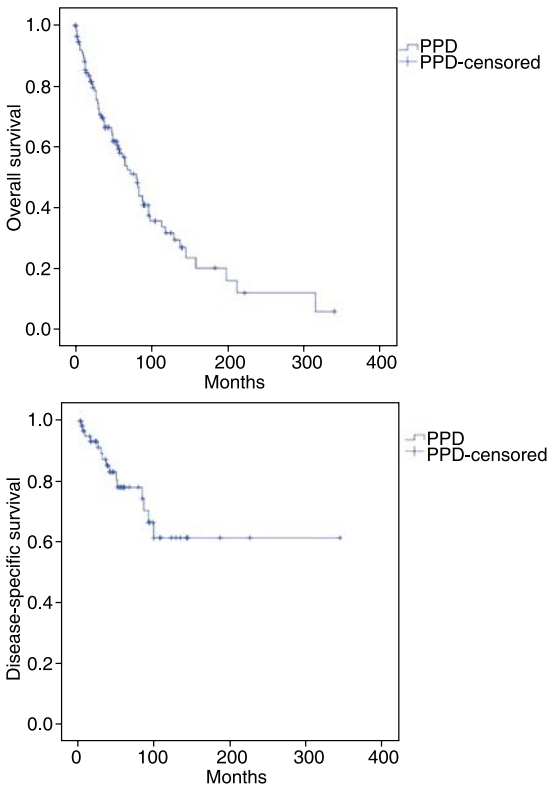


**Fig. 1** Overall survival and disease-specific survival of patients with perianal Paget's disease (PPD)

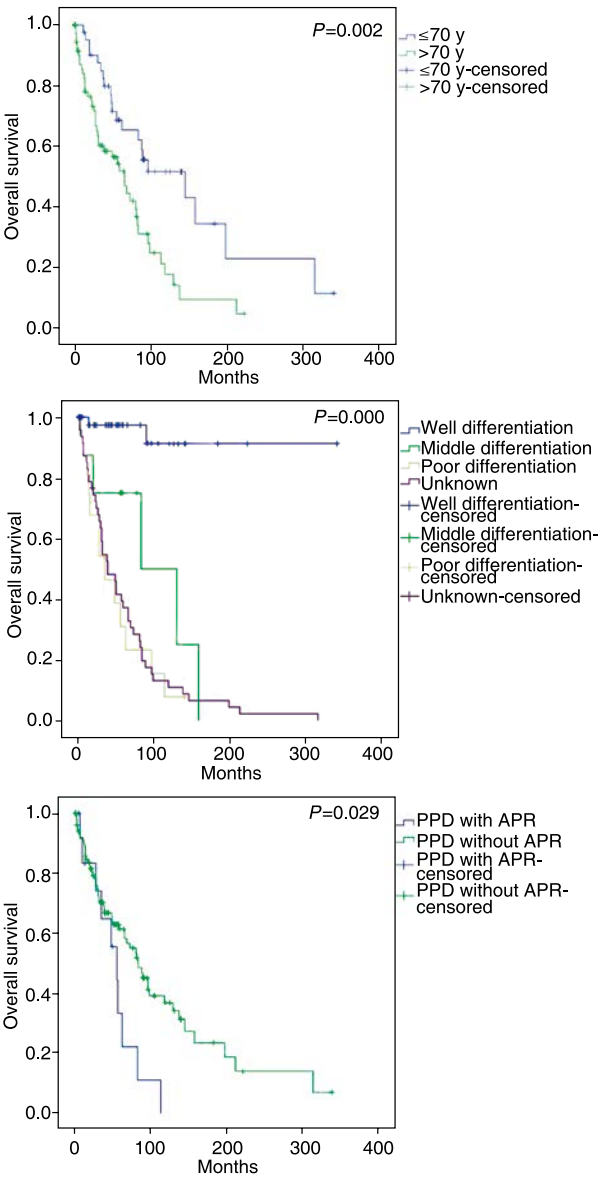


**Fig. 2** Prognosis analysis of patients with perianal Paget's disease (PPD). Age at diagnosis, grade of differentiation, and surgical method had a significant influence on the survival of patients with PPD

## Discussion

Although it is the second most common site of EMPD [5, 9], PPD is still rare. To examine the clinical features of PPD, we went through the SEER database and found 116 patients over 40 years old (1975–2015) with PPD. As far as we know, this is the largest study on PPD. The majority of patients were elderly, with the median age of onset being 73 years old. PPD is generally accepted to occur in older people [10]. Our results had an equal gender distribution (50% were male, and 50% were female). Since it is a nationwide population-based study, we do not observe the same female gender predominance as some studies [11–12].

We found that age, grade of differentiation, and surgical method were the risk factors of the overall survival of PPD patients. Patients older than 70 years old had a reduced survival rate. Older patients have a higher incidence of comorbidities and lower performance status or Karnofsky score, which might be the underlying reason for their inferior survival. The grade was the only pathology stratification included in the database. The survival rates of different grades showed satisfactory discrimination, where better-differentiated tumors resulted in more prolonged survival. Several studies have emphasized the important role of pathology. Invasive malignancy was seen to result in reduced survival [10, 13]. Takamichi [14] investigated 155 EMPDs and indicated that a tumor thickness of more than 3 mm was the cutoff point for survival.

EMPD is well known for being associated with concurrent malignancies [9, 13]. Among all anatomic sites of EMPD, PPD is an intractable neoplasm and is more frequently associated with other malignant diseases than any other EMPD. Along with the findings of our study, nearly 50% of those with PPD (56/116) have other malignancies, and over 22.41% of those have

**Table 2** Prognosis analysis of all the PPD patients

| Clinical characteristics | | 1-year survival rate [% (*n*)] | 3-year survival rate [% (*n*)] | 5-year survival rate [% (*n*)] | 10-year survival rate [% (*n*)] | 15-year survival rate [% (*n*)] | $\chi^2$ | *P* |
|---|---|---|---|---|---|---|---|---|
| Total number | | 70.69 (82) | 48.28 (56) | 31.03 (36) | 10.34 (12) | 3.45 (4) | | |
| Age at diagnosis (years) | ≤ 70 | 95.24 (40) | 78.57 (33) | 50.00 (21) | 23.81 (10) | 9.52 (4) | 9.453 | 0.002 |
| | > 70 | 77.03 (57) | 47.30 (35) | 29.73 (22) | 6.76 (5) | 2.70 (2) | | |
| Sex | Male | 84.48 (49) | 56.90 (33) | 36.21 (21) | 12.07 (7) | 5.17 (3) | 1.768 | 0.184 |
| | Female | 82.76 (48) | 60.34 (35) | 37.93 (22) | 13.79 (8) | 5.17 (3) | | |
| Race | White | 83.67 (82) | 57.14 (56) | 36.73 (36) | 12.24 (12) | 4.08 (4) | 0.204 | 0.903 |
| | Black | 100.00 (3) | 66.67 (2) | 66.67 (2) | 0 (0) | 0 (0) | | |
| | Other | 85.71 (12) | 71.43 (10) | 42.86 (6) | 21.43 (3) | 14.29 (2) | | |
| Primary site | Anus | 81.82 (54) | 56.06 (37) | 33.33 (22) | 10.61 (7) | 4.55 (3) | 2.821 | 0.244 |
| | Anal canal | 80.56 (29) | 52.78 (19) | 36.11 (13) | 8.33 (3) | 2.78 (1) | | |
| | Overlap rectum | 100.00 (14) | 85.71 (12) | 57.14 (8) | 35.71 (5) | 14.29 (2) | | |
| Grade | I (well diff) | 75.00 (3) | 50.00 (2) | 50.00 (2) | 0 (0) | 0 (0) | 46.557 | 0.000 |
| | II (mid diff) | 100.00 (4) | 100.00 (4) | 50.00 (2) | 25.00 (1) | 0 (0) | | |
| | III (poor diff) | 100.00 (8) | 50.00 (4) | 37.50 (3) | 12.50 (1) | 0 (0) | | |
| Stage | Localized | 83.67 (41) | 65.31 (32) | 36.73 (18) | 14.29 (7) | 6.12 (3) | 3.920 | 0.270 |
| | Regional | 85.71 (18) | 61.90 (13) | 38.10 (8) | 9.52 (2) | 0 (0) | | |
| | Distant | 60.00 (3) | 60.00 (3) | 40.00 (2) | 0 (0) | 0 (0) | | |
| | Unknown | 85.37 (35) | 48.78 (20) | 36.59 (15) | 14.63 (6) | 7.32 (3) | | |
| Surgical method | APR | 76.92 (10) | 53.85 (7) | 23.08 (3) | 0 (0) | 0 (0) | 4.790 | 0.029 |
| | not APR | 84.47 (87) | 59.22 (61) | 38.83 (40) | 14.56 (15) | 6.80 (7) | | |
| Survival status | Alive | 86.00 (43) | 68.00 (34) | 38.00 (19) | 16.00 (8) | 6.00 (3) | | |
| | Paget's disease | 80.00 (12) | 46.67 (7) | 26.67 (4) | 0 (0) | 0 (0) | | |
| | Others | 82.35 (42) | 52.94 (27) | 39.22 (20) | 13.73 (7) | 5.88 (3) | | |
| Total number of *in situ*/ malignant tumors for patient | < 3 | 82.22 (74) | 54.44 (49) | 34.44 (31) | 11.11 (10) | 3.33 (3) | 3.755 | 0.053 |
| | ≥ 3 | 88.46 (23) | 73.08 (19) | 46.15 (12) | 19.23 (5) | 11.54 (3) | | |

multiple primary neoplasms (3 or more). We discovered 56 PPDs with different concurrent diseases, including anorectal carcinoma (27/56), urogenital tumor (11/56), breast cancer (6/56), gynecologic tumor (6/56), and colon cancer (3/56). The most common malignancy was rectal adenocarcinoma. Grow *et al* [15] reported that 76% of those with PPD had underlying rectal carcinoma. However, we assume that this is overestimated because our data did not show such a high prevalence (21/116, 18.1%). Derived from a well-regarded system, we believe that this incidence rate is more objective and closer to the accurate morbidity [16].

Two types of PPD are typically identified [17]. Primary PPD is an *in situ* cutaneous intraepithelial neoplasm of the Paget's cell with $CK7^+/CK20^-/GCDFP15^+$ [18]. Secondary PPD shows endodermal differentiation of the gastrointestinal glands with $CK7^{\pm}/CK20^+/GCDFP15^-$ and is considered to be the epidermotropic spread of concurrent primary malignancy [18–19]. Although we could not access the detailed pathological information, we did have access to the PPD sequence and whether the patient had concurrent anorectal carcinoma. About 74.07% (20/27) of the patients were synchronous, while only 18.52% (5/27) were metachronous. We assume that those synchronous patients had secondary PPD.

For most patients that have PPD without anorectal carcinoma, wide local excision is the recommended procedure. However, 2 steps of screening are still useful. Step 1: carefully search for the presence of primary gastrointestinal lesions to avoid a misdiagnosis. Step 2: closely follow up and be aware of the possibility of metachronous gastrointestinal cancer. Wietfeldt *et al* developed a guideline for various perianal malignancies, including treatment recommendations for PPD according to the different status of the lesion and other associated malignancies [4] (Table 6). However, these are not evidence-based treatment strategies. The number of patients treated in each instance is small, which means that the use of these modalities in treating PPD remains controversial. Based on the cause of death, anorectal carcinoma is more life-threating than PPD (9/27 vs. 4/27). However, it is interesting to find that not all the candidates were following the management plan recommended. Sixteen (76.19%) patients underwent local excision of the lesion, while only 4 patients underwent APR. Surprisingly, the 4 patients who underwent APR treatment showed an inferior survival rate to the others. The underlying reason might be a histopathological error. However, more in-depth research is required. Although we were not able to check the TNM stage or histopathology, it is uncertain

**Table 3** Characters of PPD patients with anorectal carcinoma included in this study

| Clinical characteristics | Number | Percentage (%) |
|---|---|---|
| Total PPD patients with anorectal carcinoma | 27 | 100.00 |
| Age at diagnosis (years) | | |
| ≤ 70 | 10 | 37.04 |
| > 70 | 17 | 62.96 |
| Sex: Male | 16 | 59.26 |
| Female | 11 | 40.74 |
| Race: White | 22 | 81.48 |
| Black | 1 | 3.70 |
| Other | 4 | 14.81 |
| Primary site: Anus | 16 | 59.26 |
| Anal canal | 5 | 18.52 |
| Overlap rectum | 6 | 22.22 |
| Stage | | |
| Localized | 9 | 33.33 |
| Regional | 10 | 37.04 |
| Distant | 2 | 7.41 |
| Unknown | 6 | 22.22 |
| Total number of *in situ*/malignant tumors for patient | | |
| 1 | 11 | 40.74 |
| 2 | 7 | 25.93 |
| ≥ 3 | 9 | 33.33 |
| Surgery | | |
| Yes | 21 | 77.78 |
| No | 6 | 22.22 |
| Surgical method | | |
| Excisional biopsy, local tumor excision | 16 | 76.19 |
| APR | 4 | 19.05 |
| Polypectomy | 1 | 4.76 |
| Reason of no cancer-directed surgery | | |
| Not recommend | 5 | 83.33 |
| Recommend, but not performed | 1 | 16.67 |
| Radiation | | |
| No radiation and/or cancer-directed surgery | 21 | 77.78 |
| Ratiation after surgery | 4 | 14.81 |
| Ratiation before and after surgery | 1 | 3.70 |
| Ratiation prior to surgery | 1 | 3.70 |
| Chemotherapy | | |
| Yes | 9 | 33.33 |
| No/unknown | 18 | 66.67 |
| Survival status | | |
| Alive | 11 | 40.74 |
| Paget's disease | 4 | 14.81 |
| Others (not by Paget's disease) | 12 | 44.44 |
| Cause of death | | |
| Rectum and rectosigmoid junction malignancy | 7 | 43.75 |
| Anus malignancy | 2 | 12.50 |
| Cerebrovascular disease | 2 | 12.50 |
| Vulva disease | 1 | 6.25 |
| Chronic liver disease | 1 | 6.25 |
| Other causes | 3 | 18.75 |
| Sequence at diagnosis | | |
| Synchronous | 20 | 74.07 |
| Anorectal carcinoma ahead | 2 | 7.41 |
| PPD ahead | 5 | 18.52 |

**Table 5** Characters of PPD patients with other malignant tumor(s) included in this study

| Clinical characteristics | Number | Percentage (%) |
|---|---|---|
| Total number | 56 | 100.00 |
| Age at diagnosis (years) | | |
| ≤ 70 | 29 | 51.79 |
| > 70 | 27 | 48.21 |
| Sex | | |
| Male | 31 | 55.36 |
| Female | 25 | 44.64 |
| Race | | |
| White | 47 | 83.93 |
| Black | 3 | 5.36 |
| Other | 6 | 10.71 |
| Sequence at diagnosis | | |
| PPD ahead | 8 | 14.29 |
| Other malignant carcinoma ahead | 18 | 32.14 |
| Synchronous | 30 | 53.57 |
| Survival status | | |
| Alive | 20 | 35.71 |
| Paget's disease | 10 | 17.86 |
| Others | 26 | 46.43 |
| Total number of *in situ*/malignant tumors for patient | | |
| 2 | 31 | 55.36 |
| 3 | 18 | 32.14 |
| 4 | 6 | 10.71 |
| 5 | 1 | 1.79 |
| Number of PPD(s) | | |
| 1 | 47 | 83.93 |
| 2 | 8 | 14.29 |
| 4 | 1 | 1.79 |
| With other malignant tumor(s) | | |
| Carcinoma (rectum) | 21 | 37.50 |
| Adenocarcinoma (anal canal) | 4 | 7.14 |
| Adenocarcinoma (anus) | 2 | 3.57 |
| Clear cell adenocarcinoma (kidney) | 1 | 1.79 |
| Adenocarcinoma (prostate) | 7 | 12.50 |
| Carcinoma (bladder) | 3 | 5.36 |
| Adenocarcinoma (breast) | 6 | 10.71 |
| Adenocarcinoma (corpus uteri) | 2 | 3.57 |
| Granulosa cell tumor (ovary) | 2 | 3.57 |
| Mucinous adenocarcinoma (vagina) | 1 | 1.79 |
| Adenocarcinoma (vulva) | 1 | 1.79 |
| Adenocarcinoma (colon) | 3 | 5.36 |
| Adenocarcinoma (splenic flexure) | 1 | 1.79 |
| Chronic lymphocytic leukemia/small lymphocytic lymphoma (bone) | 1 | 1.79 |
| *In situ* (trunk) | 2 | 3.57 |
| Large cell carcinoma (lung) | 2 | 3.57 |
| Malignant melanoma (shoulder) | 1 | 1.79 |
| Adenocarcinoma (pancreas) | 1 | 1.79 |
| Gastrointestinal stromal sarcoma (stomach) | 1 | 1.79 |
| *In situ* (overlapping lesion of skin) | 1 | 1.79 |
| Lentigo maligna melanoma (ear) | 1 | 1.79 |
| Extranodal marginal zone lymphoma of mucosal-assoc. lymphoid tissue-MALT | 1 | 1.79 |

**Table 4** Analysis of influencing factors of PPD patients with anorectal carcinoma

| Clinical characteristics | | PPD with anorectal carcinoma [% (*n*)] | PPD without anorectal carcinoma [% (*n*)] | $\chi^2$ | *P* |
|---|---|---|---|---|---|
| Total number | | 100.00 (27) | 100.00 (89) | | |
| Age at diagnosis (years) | ≤ 70 | 37.04 (10) | 35.96 (32) | 0.010 | 0.918 |
| | > 70 | 62.96 (17) | 64.04 (57) | | |
| Sex | Male | 59.26 (16) | 47.19 (42) | 1.207 | 0.272 |
| | Female | 40.74 (11) | 52.81 (47) | | |
| Race | White | 81.48 (22) | 85.39 (76) | 0.304 | 0.859 |
| | Black | 3.70 (1) | 2.25 (2) | | |
| | Other | 14.81 (4) | 12.36 (11) | | |
| Primary site | Anus | 59.26 (16) | 56.18 (50) | 4.817 | 0.090 |
| | Anal canal | 18.52 (5) | 34.83 (31) | | |
| | Overlap rectum | 22.22 (6) | 8.99 (8) | | |
| Stage | Localized | 33.33 (9) | 44.94 (40) | 10.127 | 0.018 |
| | Regional | 37.04 (10) | 12.36 (11) | | |
| | Distant | 7.41 (2) | 3.37 (3) | | |
| | Unknown | 22.22 (6) | 39.33 (35) | | |
| Total number of *in situ*/ malignant tumors for patient | 1 | 40.74 (11) | 38.20 (34) | 3.408 | 0.182 |
| | 2 | 25.93 (7) | 42.70 (38) | | |
| | ≥ 3 | 33.33 (9) | 19.10 (17) | | |
| Surgery | Yes | 77.78 (21) | 91.01 (81) | | |
| | No | 22.22 (6) | 39.33 (35) | | |
| Surgical method | Excisional biopsy, local tumor excision | 76.19 (16) | 37.04 (30) | 12.245 | 0.007 |
| | APR | 19.05 (4) | 11.11 (9) | | |
| | Polypectomy | 4.76 (1) | 0 (0) | | |
| | Others | 0 (0) | 25.93 (21) | | |
| Reason of no cancer-directed surgery | Not recommend | 83.33 (5) | 62.86 (22) | 0.157 | 0.692 |
| | Recommend, but not performed, patient refused | 16.67 (1) | 20.00 (7) | | |
| Survival status | Alive | 40.74 (11) | 43.82 (39) | 0.144 | 0.931 |
| | Paget's disease | 14.81 (4) | 12.36 (11) | | |
| | Others (not by Paget's disease) | 44.44 (12) | 43.82 (39) | | |
| Cause of death | Rectum and rectosigmoid junction malignancy | 43.75 (7) | 26.00 (13) | 8.977 | 0.254 |
| | Colon malignancy | 0 (0) | 10.00 (5) | | |
| | Other malignancy (anus, breast, lung, bronchus, non-melanoma skin malignancy or Hodgkin lymphoma) | 12.50 (2) | 24.00 (12) | | |
| | Cardio-cerebrovascular disease | 12.50 (2) | 20.00 (10) | | |
| | Urogenital diseases (urinary bladder, vulva, or prostate disease) | 6.25 (1) | 4.00 (2) | | |
| | Septicemia | 0 (0) | 6.00 (3) | | |
| | Chronic liver disease | 6.25 (1) | 0 (0) | | |
| | Other causes | 18.75 (3) | 10.00 (5) | | |

**Table 6** Staging and treatment for perianal Paget's disease [4]

| Stage | Description | Therapy |
|---|---|---|
| I | Paget's cells found in perianal epidermis and adnexa without primary carcinoma | Wide local excision |
| IIA | Cutaneous Paget's disease without associated adnexal carcinoma | Wide local excision |
| IIB | Cutaneous Paget's disease with associated anorectal carcinoma | Abdominoperineal resection |
| III | Paget's disease in which associated anorectal carcinoma has spread to regional nodes | Inguinal node dissection, abdominal perineal resection |
| IV | Paget's disease with distant metastases of associated carcinoma | Chemotherapy, radiotherapy, local palliative treatment |

whether APR is the standard treatment of PPD with/without anorectal carcinoma.

More patients underwent chemotherapy (9/27) than radiotherapy (6/27) after surgical excision. Radiation therapy has been proposed as an adjuvant or salvage treatment of PPD [20–21]. Chemoradiotherapy and/or systemic chemotherapy are usually used for treating invasive or metastases diseases [22–25]. However, no improvements in survival were found when chemoradiotherapy was used. Karam [6] reported a surprising result of short disease-specific survival of EMPD after the application of radiotherapy. These poor adjuvant treatment results warrant further investigation. Lian *et al* [26] reported 8 cases of PPD with anorectal carcinoma, in which mucinous adenocarcinomas and signet ring cell cancer were the common histopathologic features. Highly aggressive subtypes might be indirect evidence that radio-chemotherapy has a limited effect on prolonging survival. Based on the homology with breast cancer and a similar regimen [27], Watanabe [28] has reported a successful case of EMPD with trastuzumab monotherapy on an HER-2 positive lesion after surgery. The application of a monoclonal antibody might be helpful in the future.

The 16.07% (9/56) of the patients with PPD had multiple lesions. Takamichi *et al* [14] reported that 12.4% of those with EMPD had multiple lesions or tumors spreading over two anatomic sites. No difference was found in the survival analysis by comparing these with single lesion PPD and multiple PPDs along with Paget's in other sites. However, local recurrence may be higher [14] and has been seen to be as high as 60% for a single lesion.

Any investigation of PPDs as a separate entity is very challenging because of the relative rarity of the condition. This limits the ability to detect statistically significant survival differences among subgroups. The main limitation of this study is that the SEER database lacks detailed pathology and incomplete information on the TNM stage, surgical method, and chemo/radiotherapy regimen. These factors should be taken into account when examining the results of this study.

In summary, the disease specific mortality of patients with PPD is low. Being elderly (> 70 years old), the grade of differentiation and surgical method (APR) were unfavorable risk factors to prognosis. Although PPD predisposed concurrent malignancy, no survival difference was found between those patients with one PPD and those with multiple lesions. Further investigation of patients with PPD and anorectal carcinoma is required due to a lack of research, the empirical guideline, and controversy surrounding adjuvant treatment.

## Conflicts of interest

The authors indicated no potential conflicts of interest.

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**DOI 10.1007/s10330-020-0400-0**
**Cite this article as:** Peng H, Liu ZM, Ghoorun RA, *et al*. Clinical characteristics and survival outcomes of perianal Paget's disease: A SEER population-based study. Oncol Transl Med, 2020, 6: 1–9.