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# Conditions Associated with Wound Healing Complications After Adjuvant Radiotherapy in Patients with Non-Melanoma Skin Cancer: A Retrospective Analysis

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**Abstract:** In the treatment of highly malignant skin tumors postoperative radiotherapy may be indicated after wound closure. In the University Hospital Carl Gustav Carus Dresden, Germany, a retrospective study of 75 patients, who received postoperative radiotherapy after wound closure, was conducted. In all 75 patients (56 male, 19 female), radical doses of irradiation (40-70 Gy in 20–35 fractions) were administered. The median time interval between surgery and radiation therapy was 7 weeks (range 3-48 weeks). The incidence of wound healing complications (WHCs) increased after radiotherapy ($p<0.001$). Univariable analysis showed that WHCs were associated with immunosuppression ($p=0.002$), split thickness skin graft ($p=0.007$) lymphoma or leukemia ($p=0.032$) and diabetes mellitus ($p=0.046$). Multivariable logistic regression showed that independent risk factors for WHCs were split thickness skin transplantation (odds ratio: 3.85, 95% confidence interval (CI): 1.13–13.1, $p=0.031$) and immunosuppression (odds ratio: 4.69, 95% CI: 1.18–18.7, $p=0.029$). The authors observed no association between surgical site infections and WHCs ($p=1.0$). Univariable analysis showed that SSIs were associated with leukemia or lymphoma ($p=0.019$). Together, the results show an increased incidence of WHCs after radiotherapy. Other conditions associated with WHCs were leukemia or lymphoma and diabetes mellitus. Immunosuppression and split thickness skin transplantation were independent risk factors for WHCs.

**Keywords:** Non-melanoma Skin Cancer, Wound Healing Complications, Adjuvant Radiotherapy, Wound Closure Techniques, Diabetes Complications, Retrospective Studies

## 1. Introduction

Rarely, WHCs occur after dermatosurgery [1-7]. In the University Hospital Carl Gustav Carus Dresden, Germany, approximately 3,000 patients are operated annually due to skin cancer. For highly malignant skin tumors like Merkel cell carcinoma, cutaneous sarcomas and high-risk squamous cell carcinoma, a reasonably large safety margin (1 – 2 cm) is applied to reduce the risk of local recurrence [8, 9]. In most cases, primary wound closure is not possible because of the localization and defect size. Therefore, elaborate flap

techniques or skin grafts are often used. After surgery, adjuvant radiotherapy may be necessary to reduce the risk of recurrence [8-10] Extensive defect closure and postoperative irradiation can influence wound healing [1-7] From January 1, 2016, to December 31, 2020, 75 patients underwent postoperative irradiation due to non-melanoma skin cancer (NMSC) in the University Hospital Carl Gustav Carus Dresden, Germany. The authors collected data from the patients to investigate the frequency of postoperative WHCs in the patient collective and to determine potential risk factors.

## 2. Method

The study was conducted in accordance with the Declaration of Helsinki and with approval of the local Ethics committee (BO-EK-504112020). Patient's written consent to assess their medical record data, including the use of images, for scientific reasons was obtained during their clinical visits.

Records were investigated for all patients with NMSC who were treated at the Department of Dermatology, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany, between January 1, 2016, and December 31, 2020. Patients were included in the analysis if they were at least 18 years of age and had undergone surgical treatment of NMSC followed by adjuvant radiation therapy.

Data on patient demographics (age at surgical resection, gender), characteristics of NMSC disease (pathology report, localization of the tumor) were collected from electronic medical records (Table 1). Furthermore, characteristics of wound healing (extent of resection, surgical site infection (SSI), occurrence of a wound healing complication (WHC) before or after irradiation, the need for additional surgery), applied wound closure techniques were analyzed (Table 1). Moreover, information about adjuvant radiation therapy (total radiation dose, time interval between surgery and radiation therapy), and other medical information of interest (presence of diabetes, leukemia or lymphoma, immunosuppressive drugs) were collected (Table 1). Data also included medical records from the regular follow-up examinations that each patient usually received after 3 - 6 months. In cases of WHCs, the follow-up was performed earlier.

***Table 1.*** *Patient characteristics and univariable analysis of characteristics associated with WHCs and SSIs.*

| **Characteristics complications** | **Wound healing** | | | | **Surgical site infection** | | |
|---|---|---|---|---|---|---|---|
| | **Patients, n (%)** | **Yes n (%)** | **No n (%)** | **P value (test) *** | **Yes n (%)** | **No n (%)** | **P value (test) *** |
| Gender | | | | | | | |
| Male | 56 (75) | 14 (74) | 42 (75) | | 6 (75) | 50 (75) | |
| Female | 19 (25) | 5 (26) | 14 (25) | 0.91[a] | 2 (25) | 17 (25) | 1.0[b] |
| Pathological diagnosis | | | | | | | |
| Squamous Cell Carcinoma | 42 (37) | 14 (74) | 28 (41) | | 4 (50) | 38 (57) | |
| Merkel Cell Carcinoma | 28 (56) | 5 (26) | 23 (50) | 0.15[a,*] | 3 (38) | 25 (37) | 1.0[b,*] |
| Pleomorphic Dermal Sarcoma | 1 (1) | 0 | 1 (2) | | 0 | 1 (1) | |
| Angiosarcoma | 1 (1) | 0 | 1 (2) | | 0 | 1 (1) | |
| Basal Cell Carcinoma | 2 (3) | 0 | 2 (4) | | 1 (12) | 1 (1) | |
| Porocarcinoma | 1 (1) | 0 | 1 (2) | | 0 | 1 (1) | |
| Wound Closure Technique | | | | | | | |
| Primary wound closure | 18 (24) | 2 (11) | 16 (29) | | 0 | 18 (27) | |
| Split thickness skin graft | 28 (37) | 12 (63) | 16 (29) | | 4 (50) | 24 (36) | |
| Skin flap | 27 (36) | 4 (21) | 23 (41) | 0.017[b,*] | 4 (50) | 23 (34) | 0.23[b,*] |
| Interpolated flap | 1 (1) | 0 | 1 (2) | | 0 | 1 (1) | |
| Skin graft and skin flap | 1 (1) | 1 (5) | 0 | | 0 | 1 (1) | |
| Placement of tumor | | | | | | | |
| Face | 30 (40) | 4 (21) | 26 (46) | | 4 (50) | 26 (39) | |
| Upper head | 18 (24) | 5 (26) | 13 (23) | | 2 (25) | 16 (24) | |
| Ears | 8 (11) | 3 (16) | 5 (9) | | 1 (12) | 7 (10) | |
| Upper limb | 13 (17) | 4 (21) | 9 (16) | | 0 | 13 (19) | |
| Lower limb | 5 (7) | 2 (11) | 3 (5) | 0.43[b] | 1 (12) | 4 (6) | 0.69[b] |
| Trunk | 1 (1) | 1 (5) | 0 | | 0 | 1 (1) | |
| Diabetes mellitus | 22 (29) | 9 (47) | 13 (23) | 0.046[a] | 2 (25) | 20 (30) | 1.0[b] |
| Leukemia or lymphoma | 12 (16) | 6 (32) | 6 (11) | 0.032[a] | 4 (50) | 8 (12) | 0.019[b] |
| Immunosuppression | 14 (19) | 8 (42) | 6 (11) | 0.002[a] | 0 | 14 (21) | 0.34[b] |
| Characteristics | All patients, Median (range) | WHC Median (range) | No WHC Median (range) | p value (test) * | SSI Median (range) | No SSI Median (range) | p value (test) * |
| Age (years) | 77 (49 – 95) | 78 (49 – 89) | 77 (50 – 95) | 0.72 [c] | 82 (63 – 86) | 78 (49 – 95) | 0.50 [c] |
| Size of defect ($cm^2$) | 13 (1 – 390) | 13 (1 –390) | 13 (1 –267 | 0.37 [c] | 18 (8– 80) | 12 (1 –390) | 0.47 [c] |
| Time interval between surgery and radiotherapy (weeks) | 7 (3 – 48) | 8 (3 – 24) | 7 (3 – 48) | 0.19 [c] | 9 (4 – 48) | 7 (3 – 24) | 0.44 [c] |

[a] $\chi^2$-Test; [b] Fisher's Exact Test; [c] Mann Whitney U-Test. Bold values indicate statistically significant data (p<.05). * Groups with less than 5 patients were excluded for the test.

Statistical analysis was performed using SPSS (Version 27, IBM Corporation, Armonk, NY). Tests were two-sided, with a threshold of $p<0.05$ for statistical significance. To explore differences in demographic and medical patient

characteristics between NMSC patients with and without WHCs, and with and without SSIs the chi-squared test or Fisher's exact test were used (Table 1). Fisher's exact test was applied in case of less than 5 patients in one or both groups and a dichotomous variable. The Mann-Whitney U-test was used to determine differences in age, the size of the wound, and the time to initial irradiation. Cramér's V and a chi-squared test was calculated to assess the correlation between the statistically significant parameters. These parameters were combined in a multivariable logistic regression model to predict the occurrence of WHC.

To examine the relationship between radiotherapy and WHCs, a binomial test was performed, excluding all patients with WHCs before radiotherapy. It was tested if the probability was significantly different from zero that patients without a WHC post-operation would develop WHC during radiation treatment over the course of 3 to 48 weeks.

# 3. Result

Seventy-five patients (female 19, male 56) met the inclusion criteria for the analysis. The median age was 77 years (range 49 - 95 years). Seventy-four patients underwent radical excision of the tumor and primary wound closure. For one patient, wound closure was carried out following vacuum assisted closure therapy (VAC-therapy). Radiotherapy was delivered with a median radical dose of 60 Gy (range 40 – 70 Gy) in 20-35 fractions over a period of 21 – 45 days.

## *3.1. Description and Univariable Analysis of Differences Between NMSC Patients with and Without WHC*

After radiotherapy, WHC was observed in 19 patients, of which 8 had already exhibited a WHC before irradiation. The increase by 11 patients was statistically significant ($p<0.001$).

In 14 patients with WHCs, the wounds healed with conservative management (Figure 1). In the remaining five patients, additional surgery was necessary (split thickness skin graft, wound debridement with VAC-therapy, skin flap) (Figures 2 and 3). It was not necessary to interrupt the radiotherapy in any patient. However, following a severe local reaction including bleeding, one patient was admitted to hospital so that the irradiation could be continued under close medical supervision.

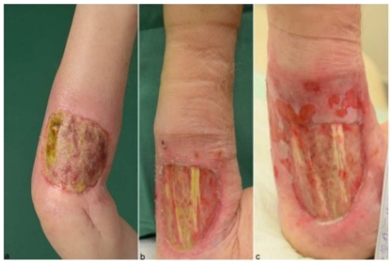

***Figure 1.*** *85-year-old patient with Merkel cell carcinoma with lymph angioinvasion on the right forearm a) 4 months after radiotherapy; b) 11 months after radiotherapy; c) 13 months after radiotherapy.*

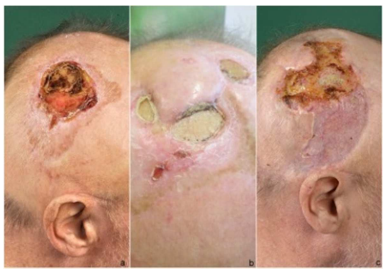

***Figure 2.*** *70-year-old patient with squamous cell carcinoma occipital with perineural tumor spread and subcutaneous lymph node metastasis: a) 6 months after radiotherapy; b) 15 months after radiotherapy and 8 months after wound closure with transposition flap plasty and closure of the secondary defect with split thickness skin transplantation; c) 31 months after radiotherapy and 6 months after wound closure with enhancement flap and closure of the secondary defect with split thickness skin graft.*

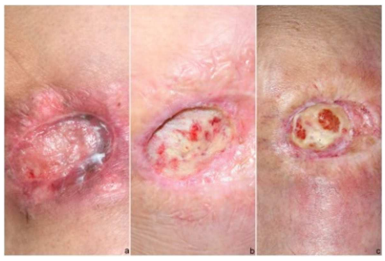

***Figure 3.*** *68-year-old patient with Merkel cell carcinoma with lymph angioinvasion on the right knee a) 3 months after radiotherapy; b) 12 months after radiotherapy; c) 17 months after radiotherapy and 5 months after VAC-therapy and wound debridement.*

Possible factors associated with postoperative wound healing like surgical site, technique of wound closure, defect size, and tumor entity were examined. In patients with a WHC, the tumors were less common in the face compared to patients without a WHC (21% vs 46%). Conversely, WHCs tended to occur more often in tumors on the upper head, ears, limbs, and trunk. None of these differences were significant (Table 1). When differentiating between different wound closure techniques, 63% of the patients with WHCs had undergone split thickness skin graft compared to 29% of the patients without WHC ($p=0.007$). Conversely, a WHC was observed less often after applying primary wound closure (11% vs 29%; $p=0.13$) or flap plasty (21% vs 41%; $p=0.17$, Table 1). The size of the defect was similar between patients with and without WHC (Median 13 cm2, $p=0.37$). In patients with a WHC, 74% had squamous cell carcinoma and 26% had Merkel cell carcinoma ($p=0.072$, Table 1). The time interval between surgery and radiation therapy ranged from 3 – 48 weeks and did not differ significantly between patients with normal and impaired wound healing (Table 1).

Furthermore, potential risk factors to assess morbidity in the cohort group like immunosuppression, leukemia or lymphoma, diabetes mellitus, and age were investigated. Fourteen patients received immunosuppressive drugs (methotrexate, mycophenolate, tacrolimus, chemotherapy, rituximab, methylprednisolone, prednisolone) due to kidney transplantation, stem cell transplantation, graft-versus-host disease, leukemia or lymphoma, chronic polyarthritis or rheumatoid arthritis. Immunosuppression was significantly

more common in patients with a WHC after irradiation (42% vs 11%; p=0.002). Twelve patients suffered from lymphoma or leukemia, which was also significantly associated with a WHC (p=0.032). Out of the patients with WHC, 47% had diabetes mellitus compared to 23% of the patients without WHC (p=0.046). Median age was similar between the groups (Table 1).

### *3.2. Correlation Analysis*

The correlations between and immunosuppression, leukemia or lymphoma, diabetes mellitus and split thickness skin grafting turned out to be low (V<0.26). Still, the correlation between diabetes mellitus and split thickness skin transplantation (V=0.229, p=0.047) and the correlation between lymphoma or leukemia and immunosuppression (V=0.258, p=0.026) were significant.

### *3.3. Binary Regression Analysis*

Binary logistic regression analysis identified split thickness skin grafting (Odds ratio: 3.85, 95% confidence interval (CI): 1.13 – 13.1) and immunosuppression (Odds ratio: 4.69, 95% CI: 1.18 – 18.7) as independent risk factors for developing postoperative WHC in the considered NMSC patient cohort after adjustment for diabetes and leukemia or lymphoma (Table 2).

### *3.4. Description and Univariable Analysis of Differences Between NMSC Patients with and Without SSI*

Eight patients received postoperative antibiotic therapy due to SSIs, 25% developed a WHC; no association between these conditions was observed (p=1.0). There was also no statistically significant association between early postoperative WHC (before radiotherapy) and SSI (p=0.585). None of the patients had critical infections or sepsis. Seven patients received oral antibiotics, while one patient received antibiotics intravenously. Further three patients without SSI received prophylactic antibiotic therapy, one of them developed a WHC. To the best of the authors' knowledge, there were no additional SSIs after radiation.

***Table 2.*** *Multivariable binary logistic regression for the development of WHCs.*

| Characteristics | P value | Odds ratio | 95% confidence interval |
|---|---|---|---|
| Split thickness skin graft | 0.031 | 3.85 | 1.13 – 13.1 |
| Diabetes mellitus | 0.26 | 2.03 | 0.59 – 6.99 |
| Leukemia or lymphoma | 0.19 | 2.93 | 0.60 – 14.4 |
| Immunosuppression | 0.029 | 4.69 | 1.18 – 18.7 |
| Constant | <0.001 | 0.08 | |

Covariates in the binary logistic regression model included split thickness skin graft, diabetes mellitus, leukemia or lymphoma, immunosuppression.
Nagelkerke R2: 0.304
Bold values indicate statistically significant data (p<.05).

Six men and two women developed SSIs (p=1.0). SSI was in the face, on the upper head, on the ears and one on the lower limb. In patients with SSI, 50% (vs 36% of patients without SSI) received wound closure with split thickness skin graft and 50% (vs 34%) received skin flaps. None of these factors were statistically significant (Table 1). The median size of defect was 18 cm2 in patients with SSI compared to 12 cm2 in patients without SSI (p=0.470). When differentiating between pathological diagnoses, 50% (vs 57% of patients without SSI) had squamous cell carcinoma, 38% (vs 37%) Merkel cell carcinoma and 12% (versus 1%) basal cell carcinoma (Table 1). There were no increased SSIs in patients with immunosuppression (p=0.338) and patients with diabetes mellitus (p=1.0). The authors observed a significantly higher proportion of patients with leukemia or lymphoma among patients with compared to patients without SSI (50% versus 12%, p=0.019, Table 1). Median age was similar between the groups (p=0.502).

## 4. Discussion

Highly malignant tumors usually require surgery with an extended safety margin to reduce the risk of local recurrence [8, 10, 11]. In some cases, postoperative radiotherapy is necessary for additional risk factors [8-10]. In the studied cohort, there were several reasons for postoperative radiotherapy. In Merkel cell carcinoma, according to the German association of scientific medical societies (AWMF) guideline, postoperative irradiation of the tumor bed is indicated to reduce the locoregional risk of recurrence [10]. Indications for postoperative irradiation for squamous cell carcinoma include risk factors such as perineural infiltration, locoregional metastasis and R1- or R2-resection according to the German AWMF guideline [8, 9]. Individual patients with squamous cell carcinoma were irradiated after local recurrence of the tumor [9]. The indication for postoperative radiation of basal cell carcinoma and angiosarcoma was R1-resection, and the indication for postoperative radiotherapy of porocarcinoma and pleomorphic dermal sarcoma was local recurrence [9].

For better understanding the pathogenesis of wound healing complications after radiotherapy, the physiological effects of irradiation should be considered.

Irradiation leads to hyaline degeneration, fibrosis, microvascular damage and as a result ischemia and edema [12-21]. To avoid WHCs after irradiation, one should pay attention to the vascularization of the tissue bed [6, 18, 22, 23].

Sumi et al. observed that the reaction to irradiation of rat skin generally begins at the margins and progressively extends to the center of the flap or the graft [24, 25]. It has been speculated that regions with higher vascularity and newly generated vessels might be more sensitive to radiation [24-26]. Invasion of newly generated vessels is, however, necessary for the survival of skin grafts [24]. In the present study, skin transplantation was an independent risk factor for developing WHCs after radiotherapy. Artamanova et al. also observed that full thickness skin grafts were associated with necrosis [1]. Lal et al. reported no increased WHCs after radiation in skin grafts, but the study included only 15 patients and their median age was 52 years, while the median

age in the present study was 77 years [27]. Bui et al. also reported no increased occurrence of WHCs in split thickness skin grafts after irradiation [26]. However, their patients were younger and in most cases, skin grafts were transplanted on well-vascularized muscle beds, which might have had an impact on wound healing [26].

Out of the patients without initial WHCs, 16% of 67 patients developed a WHC during or after irradiation which indicates that radiotherapy is a risk factor for WHC.

Sumi et al. discovered that the reaction of skin grafts on rats to irradiation depends on the time interval between the transplantation and radiotherapy [11, 18, 24, 28, 29]. Skin grafts that were irradiated in the early hypovascular stage (2 days) reacted mildly to moderately, those irradiated in the hypervascular stage (2 days – 3 weeks) reacted severely and those irradiated in the late hypervascular stage (3-4 weeks) reacted similarly to normal skin [18, 24, 27, 30]. They also showed a similar course for irradiated skin flaps, which reacted akin to normal skin in the late hypervascular stage (3-4 weeks) [25]. In the present study, the time interval between surgery and radiotherapy in patients that developed WHCs ranged from 3 – 24 weeks and was similar to patients without WHCs. However, it can be assumed that a reason for the delay of the postoperative radiotherapy for several months might have been slow wound healing. Individual patients were irradiated due to tumor recurrence, which explains the long intervals between surgery and radiotherapy in some cases. Significant delay of radiotherapy should be avoided because of the risk of tumor recurrence and locoregional metastasis [11, 30–33].

In addition to radiotherapy and wound closure techniques as risk factor for a WHC, possible factors associated with postoperative wound healing like surgical site, defect size, tumor entity and the occurrence of SSIs were examined.

Among the NMSC patients analyzed WHCs occurred less frequently in the facial region. It might be possible that the facial region is less susceptible to WHCs after radiation due to increased vascularization [6, 18, 22, 23]. Less vascularized wound bed (cartilage, joint proximity, exposed tendons with increased connective tissue and reduced blood circulation, galea with thin periosteum) could be a reason for the occurrence of WHC in tumors on the upper head, ears, limbs and trunk [3, 7, 18, 23].

The size of defect among patients with WHC in the present study varied between 1 cm2 and 180 cm2. There was no statistically significant connection between the development of WHC and the size of the defect. Crişan et al. found out that larger defects on the ears had more early complications like flap necrosis [4]. However, they differed between defect sizes smaller and larger than 1 cm2 which were smaller than the sizes of defects in the studied patients which ranged from 1 to 390 cm2 [4]. Moreover, the association Crişan et al. observed may not be generalizable to other surgical sites [4].

Furthermore, WHCs occurred more frequently in squamous cell carcinomas, which is in accordance with previous reports [34, 35]. However, the localization could also have an effect on wound healing.

In addition to potential risk factors for a WHC related to surgery, patient morbidity can influence postoperative outcome [1, 3–5, 7].

Whether drug-induced immunosuppression is a significant risk factor for WHC is controversial and may depend on the type of immunosuppressant and the resulting changes in the immune system [1, 2, 4, 5, 36–38]. These data indicate a significant association between WHC and immunosuppressive drugs. Crişan et al. reported no significant correlation between drug-induced immunosuppression and WHC [4]. However, only 3% of the investigated 146 patients were immunocompromised compared to 19% in the present study [4].

To assess the association of immunosuppression with WHC, both drug-related and disease-related changes in the immune system were examined.

The association between WHC and leukemia or lymphoma in the current study was statistically significant. Leukemia and lymphoma modulate the immune system and are often treated with chemotherapy or immunosuppressants; both factors could lead to impaired wound healing [39–41]. In the multivariate analysis, immunosuppression but not leukemia or lymphoma was an independent significant factor, suggesting that the effect of these diseases on wound healing might be mediated by the immunosuppressants. Furthermore, there was a statistically significant association between leukemia or lymphoma and SSI in the present study. Moreover, additional two patients who received postoperative prophylactic antibiotics to avoid SSI suffered from leukemia or lymphoma. Therefore, the association might be even stronger. Fernandez-Pineda observed no increased SSIs in children with leukemia or lymphoma after gastrostomy placement, but only children were investigated in their study [42].

In the present study, a statistically significant association between WHC and diabetes mellitus was observed. This observation is in line with the literature [5, 35, 43, 44]. Ramanujam et al. proposes that this finding might rather be due to the comorbidities of diabetics [4, 6, 45–47]. However, Baltzis et al. describe biological mechanisms of wound healing that may be affected by diabetes mellitus [44]. Individual studies reported no increased occurrence of WHC like necrosis in diabetics [1, 4]. The risk of WHC in a patient with diabetes mellitus might depend on additional comorbidities and on how well the diabetes is controlled [4, 6, 44–47].

In the University Hospital Carl Gustav Carus Dresden, Germany, the following methods to prevent WHC are used. If adjuvant radiotherapy is indicated in areas with an increased risk of WHC, the surgeon should, if possible, close the primary defect with a primary wound closure or a flap technique [3]. The secondary defect may be closed with a skin graft. The localization of the tumor and the flap design should be photo-documented, so that the radio oncologist is able to plan the irradiation. If a flap technique is not possible, wound conditioning is recommended to support the formation of granulation tissue, for example by VAC-therapy or dermis replacement product pre-transplantation [19, 20, 48, 49]. Furthermore, additional risk factors for WHC should be considered (immunosuppression, leukemia or lymphoma, and

diabetes mellitus). In the case of borderline resectable tumors, primary radiotherapy or/and systemic therapy should be discussed [50, 51].

# 5. Limitations

Limitations of the present study are the relatively small number of patients and the retrospective analysis of previously collected patient data. The analysis of a greater number of patient data might investigate further risk factors for WHC, which were not significantly correlated with WHC in this study. However, to the best of the authors' knowledge, previous studies which investigated potential risk factors for WHC after radiation therapy included much smaller patient cohorts [15, 24–27]. As the authors analyzed previously collected patient data, they relied on the documentation in the electronic medical record. If WHCs or SSIs were not documented or photographed, they were not included in the study. The subject should be further investigated in prospective studies in order to obtain more reliable data and to reduce the chance for introduction of selection and recall bias.

# 6. Conclusion

Together, the results show an increased incidence of WHCs after radiotherapy. Other conditions associated with WHCs were leukemia or lymphoma and diabetes mellitus. Immunosuppression and split thickness skin transplantation were independent risk factors for impaired wound healing. SSIs were not associated with WHC. However, there was an increase of SSIs in patients with leukemia or lymphoma. By paying attention to these potential risk factors for WHCs, an appropriate defect closure technique can be selected. For patients at increased risk of WHCs, frequent monitoring of the wounds can be performed both postoperatively and during irradiation. Prospective studies with a larger number of patients should be performed to identify other potential risk factors and evaluate methods to prevent WHCs in high-risk patients.

# Conflict of Interest

The authors have no conflict of interest to declare.

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The patients in this manuscript have given written informed consent to publication of their case details.

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