**STUDENT NAME**: Mohammad Pannu **DATE**: August 7th, 2015

**PROJECT TITLE:** Incidence and Implications of Skin Cancers in Chronic Lymphocytic Leukemia (CLL)

**PRIMARY SUPERVISOR NAME**: Dr. James B. Johnston

**DEPARTMENT**: Department of Internal Medicine

**SUMMARY**:
A recent population-based study in Manitoba showed that skin cancers are very common in chronic lymphocytic leukemia (CLL), probably as a result of immunosuppression. We have now studied 592 newly diagnosed CLL patients attending the CancerCare Manitoba CLL Clinic from 2002 until 2012. The median age at diagnosis of CLL was 67 years (range, 36-99) with a M:F ratio of 1.6:1. The median follow-up was 4.63 years (range, 0.01-11.00 years). There were 133 (22.39%) patients with skin cancers, half having skin cancers before the CLL diagnosis (pre-CLL) and half following the diagnosis (post-CLL). In the pre-CLL group, the risk of skin cancer increased 5-6 years before the CLL diagnosis indicating that immunosuppression can precede the diagnosis of CLL. For all patients, the risk of skin cancer correlated with Rai stage and duration of disease. Of 368 total skin cancers, 208 (56.52%) were basal cell carcinomas (BCC), 92 (25.00%) squamous cell carcinomas (SCC), 47 (12.77%) Bowen's disease, 18 (4.89%) melanomas, and 3 (0.82%) Merkel cell carcinomas (MCC). Multiple skin cancers occurred in half the patients. 22.72% patients died, usually from second malignancies or CLL. There were three deaths from skin cancer, two melanomas and one BCC. In summary, one-quarter of CLL patients developed skin cancer, and this was predictive for developing a solid tumor. CLL patients, particularly those with advanced Rai stage, require regular surveillance screening for other cancers, especially those of the skin.

Student Signature Supervisor Signature

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## INTRODUCTION AND BACKGROUND

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most common adult leukemia in the Western world with an age-adjusted incidence of 7.99/100,000[1]. It is characterized by an unregulated proliferation of monoclonal B lymphocytes and typically diagnosed incidentally on routine blood tests. In the population, the median age of diagnosis is 71.5 years with a male:female ratio of 1.3:1. Prognosis is highly dependent on the Rai stage at presentation, although biological markers, such as the IgVH mutational status, ZAP-70, CD38 and β2-microglobulin levels are also useful[2].

Over the past twenty years, the prognosis for CLL patients has significantly improved with the development of chemoimmunotherapy. The typical treatment regimens for younger more fit patients being FCR (fludarabine, cyclophophamide and rituximab) or chlorambucil/obinutuxumab for the elderly or less fit[2,3].

Small lymphocytic lymphoma shares similar characteristics to CLL, and only differs by the number of malignant cells in the peripheral blood, and the two are often used interchangeably. Both have been classified together under "CLL" by the World Health Organization since 2008. A non-malignant precursor to CLL or SLL is monoclonal B cell lymphocytosis (MBL), where there is a small number of CLL type cells in the peripheral blood, without any other evidence of disease. Approximately 1-2% of CLL patients progress to CLL/SLL each year[2].

Over time, there is progressive immunodeficiency in CLL, which is associated with an increased incidence of infections and second malignancies [4]. The majority of patients who attend the CLL clinic will die from progressive disease, infections or second malignancies[4–6]. However, the precise cause of death in these patients is likely changing, as chemoimmunotherapy is highly effective in reducing tumor burden, but may actually worsen the degree of immunosuppression. Thus, while fewer patients nowadays may be dying from progressive CLL, an increased number are dying from infections and second malignancies. Second malignancies in CLL are of great interest to Manitoba researchers as they presently are the leading cause of death in CLL patients (38%), followed by disease progression (35%) and opportunistic infections (15%)[5]. Thus, identifying patients who are at risk of these complications is critical, as it will allow screening for early detection and therapy, greatly reducing the number of deaths from second malignancies.

One of the first studies on second malignancies in CLL was conducted in Manitoba 40 years ago, as Manitoba is fortunate to have both population- and clinic-based data sources available to study CLL/SLL. The population study showed a three-fold increased risk of second cancers in CLL patients compared to the general population[7]. Further studies have shown similar results[8–10] all depicting a 1.5- to 2-fold increased risk of second malignancy regardless of age, gender, or treatment history. These malignancies also tend to be more aggressive, respond poorly to treatment and carry an increased risk of mortality[4,11,12]. The increased risk of subsequent cancers is primarily attributed to immune suppression from CLL, but genetic predisposition, effects of systemic therapy and surveillance bias are also thought to play a role[4].

A recent population-based study on CLL in Manitoba showed that second cancers are twice as common in this disease compared to an age- and sex-matched control population and also compared to patients with follicular lymphoma[4]. It is postulated that this is related to immunosuppression secondary to the disease and chemoimmunotherapy. This study also showed that skin cancers were the most common second malignancy (40% of all second

cancers), and the incidence was only increased after the diagnosis of CLL. However, whether these findings are relevant to patients in a CLL clinic, who are likely to be younger and receive chemoimmunotherapy, is unclear.

Skin cancers may be grouped into melanoma and non-melanoma skin cancers (NMSCs), with basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) making up the vast majority of the latter. BCCs constitute 80% of all NMSCs in Manitoba. The rates of NMSCs in Manitoba have markedly increased in the last 50 years, with fair skin and sunlight exposure being the main risk factors [13]. BCCs rarely metastasize and are easily treatable, while other forms of skin cancers such as SCC, Merkel's cell carcinoma and melanoma can spread quickly and lead to poorer survival in patients. This is especially true in immunocompromised CLL patients, who tend to have increased rates and more aggressive forms of skin cancer [4,12,14].

In the present study, we investigated the incidence and type of skin cancers in newly diagnosed CLL patients seen at the CancerCare Manitoba (CCMB) CLL Clinic over an 11-year period. It is postulated that skin cancers will occur more frequently in CLL patients as a result of immunosuppression, that the rates will increase in patients with advanced CLL on chemotherapy and that the presence of skin cancer may predict the development of other second malignancies. Moreover, the risk of skin cancers likely correlates with the presence of biological markers indicating a more aggressive disease.

## METHODS

### Patient Selection

Patients diagnosed with CLL/SLL and MBL in the CCMB CLL/SLL clinic between January 1st, 2002 to December 31st, 2012 were identified using clinic records. CLL/SLL and MBL cases were identified using the International Classification of Diseases for Oncology (ICD-10) codes. Date of CLL diagnosis, gender, vital status, date and cause of death, date and type of other cancers and treatment were obtained from Manitoba Cancer Registry.

Information on Rai stage, clinical markers (eg, CD38 and ZAP-70) and treatment were obtained from patient charts and online clinical and research databases at CCMB, known as ARIA and CAISIS, respectively. The majority of these markers were gathered from lab tests done on the same day as the same day as the CLL diagnosis. When same day results were unavailable, results were obtained from a test done within a year of the CLL diagnosis.

For patients with skin cancer, the charts and pathology reports were studied to determine when the skin cancer(s) was/were diagnosed, the type, location, and the date of excision or biopsy. In patients with no known date of diagnosis for the skin cancers, the excision or treatment dates were used which, in the majority of cases, was within a month of the diagnosis. In this study, the main types of skin cancer were as BCC, SCC and melanoma, while less common sub-types were classified under the "other" category.

Ethics approval was obtained through the University of Manitoba Research Ethics Board.

### Statistical Analyses

Logistic regression analyses was performed to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Microsoft Excel was used for data management and SAS was used to perform the statistical Analyses.

## RESULTS

### 1. Study Population

The cohort consists of 582 CLL patients diagnosed over 11 years, between January 1st, 2012 and December 31st, 2012 *(Fig. 1).* Median age at the time of CLL diagnosis was 67 years (range 36 - 99) with a M:F ratio of 1.6:1. This compares to the median age at CLL diagnosis of 71.5 years and a M:F ratio of 1.3:1 in the Manitoba CLL population. The median follow-up in this cohort was 4.63 years (range 0.01 - 11.00).

There were 131 patients (22%) with at least one skin cancer in this cohort. Of 131 patients, 67 (52%) had a single skin cancer diagnosis (32% pre-CLL and 68% post-CLL) and 64 (48%) had multiple skin cancer diagnoses (62% pre-CLL and 38% post-CLL) *(Fig. 2).*

### 2. Types of Skin Cancers and Rai Stage

There were a total of 368 skin cancers diagnosed in 131 patients *(Table 1).* Of these, 208 (56%) were BCC, 92 (25%) were SCC, 47 (13%) were Bowen's, 18 (5%) were melanomas, and three (1%) were Merkel cell carcinomas. Interestingly, multiple skin cancers with varying histologies occurred in almost half of the patients. Half of Rai stage IV patients with no prior skin cancers were eventually diagnosed with a skin cancer *(Table 2).*

### 3. Incidences of Skin Cancers in Relation to Time of CLL Diagnosis

In contrast to the population study, skin cancers in the clinic cohort were roughly split around the CLL diagnosis, both before (pre-CLL) and following the CLL diagnosis (post-CLL). In the group with pre-CLL skin cancer, the number of skin cancers started to increase 5-6 years before the CLL diagnosis suggesting that the patients were developing immunosuppression years before the diagnosis of CLL. The increasing incidence of skin cancers continued for a further 3 years after the CLL diagnosis and then declined; the decline was presumably due to the decreasing number of patients with longer follow up *(Fig. 3).* In the post-CLL group, the number of skin cancers/year also increased for 3 years following CLL diagnosis and then declined. We hope to mitigate this decline by increasing the follow up by an extra year, allowing us to see more diagnosed skin cancers.

### 4. Survival of CLL patients

Within the follow-up period, 135 patients (23%) died, with the major causes of death being CLL and second malignancies. However, the presence of skin cancers did not appear to influence survival. There were a total of three deaths due to skin cancers; two patients died of melanoma and one from BCC (Table 3).

### 5. Rai Stage and other Prognostic Markers

As shown in *Table 2*, 25% of patients had either Rai stage 0/I disease, while 65% had Rai stages III/IV disease at the time of their skin cancer diagnosis, confirming the idea that more advanced disease is implicated in skin cancer development.

CLL cases with no history of previous cancers that positively express CD38 have a more than three-fold increased risk of a skin cancer diagnosis after CLL diagnosis (OR 3.24, 95%CI 1.30 – 8.07). However, ZAP-70 expression did not show any significant association with risk of other malignancies including skin cancers. The influence of other prognostic markers on the incidence of second malignancies is presently being evaluated.

### 6. Second malignancies

As expected, the most common second malignancy in the cohort was skin cancer. Of the 131 CLL patients with at least one skin cancer, 73 (56%) developed the first skin cancer after CLL diagnosis. Median time from CLL diagnosis to the diagnosis of the first skin cancer was 3.7 years (ranging 0.5 – 11.7 years). Similarly, of 146 patients with other secondary cancers (excluding skin cancers), 70 (48%) developed the other malignancy after the CLL diagnosis, suggesting immune suppression from CLL or chemoimmunotherapy may play a role. Median time from CLL diagnosis to the diagnosis of the other malignancy was 2.6 years (ranging 0 – 11.6 years).

Forty-one CLL patients had both skin cancer and another malignancy, of which 15 (37%) developed the skin cancer prior to the other malignancy. The median time from the first skin cancer to the first non-CLL malignancy was 4.21 years (range, 0.1 – 31 years).

Patients with no history of a solid tumor, who developed a skin cancer (either pre- or post-CLL) were found to have a 24-fold increased risk of developing a solid tumor after the CLL diagnosis (23.68 95%CI 7.31 – 76.73). Thus, the presence of a skin cancer can be predictive for the development of a solid tumor in CLL. These results are still being tallied.

### 7. Chemotherapy

Seventy of the 131 skin cancer patients (53%) received chemotherapy for CLL and/or other malignancies. Ongoing analysis is looking to determine whether chemotherapy may predispose patients to developing skin cancer. Results were not available at the time of writing.

## DISCUSSION

In this study, we have demonstrated that 22% of patients attending the CLL clinic at CCMB with a median follow-up of 4-5 years developed skin cancer, and half the affected patients had multiple skin cancers of different histological types. These results confirm previous population studies from Manitoba and elsewhere, demonstrating that patients with CLL have a high incidence of skin cancer[4,15–17]. While not examined in the present study, we have previously demonstrated that the risk of skin cancer is 5-10-times higher in CLL patients than in an age- and sex-matched control population[4]. Population studies in Manitoba have demonstrated that the incidence of skin cancer has markedly increased over the years, with the likelihood of developing non-melanoma skin carcinoma (NMSC) increasing two-three-fold from

the 1970s to the 1990s[1,13,18]. This is likely related to increased sun exposure and occurs mainly in fair-skinned individuals. The two most common forms of NMSC are BCC and SCC, the former making up approximately 80% of all cases[19,20]. However, the ratio of BCC:SCC appears to be age dependent, and decreases with aging[13,18]. This change with aging may be related to the causation of these cancers, as the risk of squamous cell carcinoma is more intimately related to the duration of sun exposure than is basal cell carcinoma.

In the present study, BCC:SCC ratio was 2.26:1 which is lower than the ratio in the normal population[13]. The ratio was even lower if only patients with multiple skin cancers and chemotherapy were to be considered, at 1.19:1, suggesting that SCC is more common in patients with immunosuppression. Our patient cohort also had a large number of Bowen's disease (SCC in-situ), which could have developed into SCC and decreased this ration even further. This increased incidence of SCC in the immunosuppressed has been well documented in the literature, especially among organ-transplant patients with some studies suggesting a 65-times increased risk versus the normal population. In contrast to the normal population, organ transplant patients also tend to develop more SCC than BCC and the exact mechanism is unknown[21].

If found early, SCC can have an excellent prognosis, but for those with metastatic disease, prognosis is extremely poor with ten-year survival being less than 20 percent [21]. In our study, we only had 3 deaths primarily due to skin cancer with 2 melanomas and 1 BCC. This was not enough to specifically show a link between poor survival and SCC, but patients with SCC tended to have more aggressive disease in CLL. Ongoing studies are attempting to determine the cause of death in the 39 "unknown" patients, specifically deaths from SCC or MCC. MCCs in particular have shown to have a very poor prognosis[22–24].

An interesting and novel finding in this study was that, for patients who developed skin cancer before the diagnosis of CLL, the number of skin cancers began to increase 5-6 years before the diagnosis of CLL and continued to increase on a yearly basis *(Fig. 3)*. The increased incidence of skin cancer in CLL is thought likely related to immunosuppression, as patients receiving immune-suppressants following organ transplantation are at higher risk of developing all forms of skin cancer[8,15,16]. These findings suggest that a proportion of CLL patients have significant and clinically relevant immunosuppression for years prior to their diagnosis of CLL. Other studies would tend to support this hypothesis. For example, Tsai et al have demonstrated immunoglobulin abnormalities in the blood of CLL patients ten years prior to the diagnosis of CLL[25]. In addition, Moreira et al have shown that patients with MBL have an increased incidence of infections, compared to the normal population[26]. MBL is a precursor to CLL, and this study confirms the immune dysfunction can occur in these patients before they have overt leukemia. Furthermore, the fact that the number of skin cancers increases with the duration of CLL indicates that immune suppression is worsening over time in these patients.

In this study we attempted to identify clinical features in our patients that would predict for the development of skin cancer. Clearly, patients with MBL had a very low risk of developing skin cancer and the risk for SLL appeared to be intermediate. As expected, the majority of our patients presented with early-stage CLL (Rai 0/I) and had a low likelihood of developing skin cancer, whereas those with Rai stage III/IV were at highest risk. However, whether this is primarily related to the immune-suppression associated with advanced disease or to the chemotherapy used to treat these patients is unclear. In our population study[4], we demonstrated that chemotherapy could increase the risk of a secondary cancer two-fold in patients with CLL or follicular lymphoma, and we assume a similar effect will be seen in the clinic. However, it should be noted that in the population study patients received single agent chemotherapy,

usually chlorambucil or fludarabine, whereas most patients in the present study would have received more intensive chemotherapy, often containing rituximab. The more intensive chemotherapy is presumably more immunosuppressive, but the additional impact of rituximab on the incidence of skin and other cancers is unknown.

While it is appreciated that immunosuppression in CLL can increase the risk of cancer, and skin cancers in particular, the mechanism for this finding is unclear. Interestingly, the risk of second malignancies is not increased in follicular lymphoma, another chronic B cell disorder that is followed and treated in a similar fashion to CLL. Similarly, it is unclear why only certain CLL patients develop skin cancer, and why some patients will actually develop skin cancer prior to the diagnosis of CLL. One clue to these changes may be the direct effects of CLL cells on T cell function[27,28]. Through the interaction of CD200, CD270, CD274 and CD276 on CLL cells, both CD4+ and CD8+ cells become paralysed and it is postulated that this mechanism may explain the profound immunosuppression seen in CLL, particularly in patients with advanced disease. However, whether T cells are more impaired in CLL patients with skin or other cancers requires further study.

**Conclusion and Future Direction**

The results of this study highlight that CLL patients are at high risk of developing skin cancer and that patients with skin cancer and CLL are also at substantially higher risk of developing other solid tumours. All patients in the CLL clinic are now initially assessed by a dermatologist and those considered to be at high risk of developing further skin cancers are followed regularly. This it to allow for screening and early detection of disfiguring and potentially fatal skin cancers (Fig 4 & 5). Ongoing studies are determining which skin cancer patients are at highest risk of developing solid tumors, which will help decide which patients require the most vigilant screening methods for other cancers. Finally, ongoing studies are evaluating immune function in these CLL patients to determine if an immune abnormality can be detected and help predict the development of second malignancies.

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**Figures and Tables:**

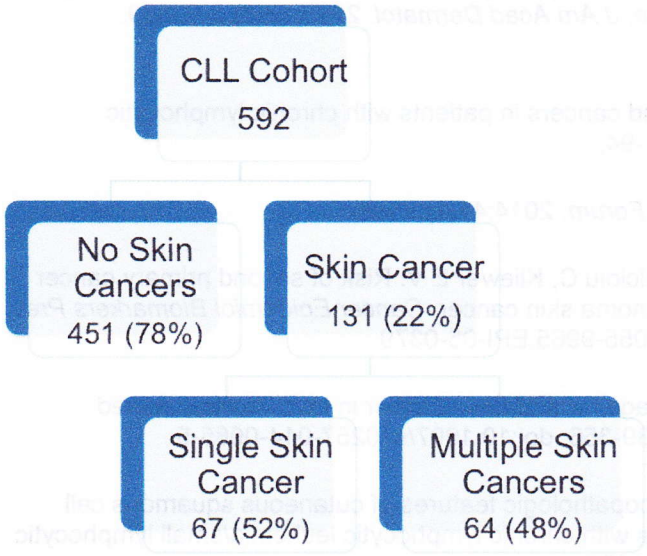


**Fig.1.** Overview of the CCMB CLL Clinic cohort and incidences of multiple and single skin cancers

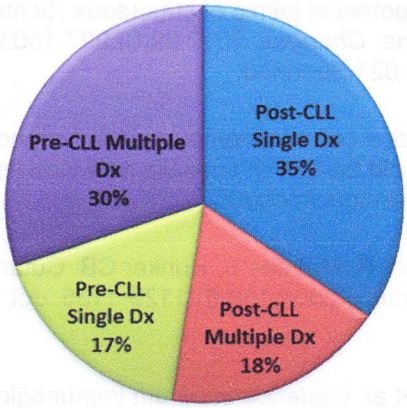


**Fig. 2**. Breakdown of pre- and post-CLL skin cancer diagnoses in patients with single or multiple skin cancers

| Type of Skin Cancer | n | % |
|---|---|---|
| Basal Cell Carcinoma | 208 | 56 |
| Squamous Cell Carcinoma | 92 | 25 |
| Bowen's Disease | 47 | 13 |
| Melanoma | 18 | 5 |
| Merkel Cell Carcinoma | 3 | 1 |
| *Total* | *368* | *100* |

**Table 1.** Type of skin cancers in CCMB CLL clinic patients

| Stage | At CLL Diagnosis | At 1st Skin Cancer (%) |
|---|---|---|
| Rai 0/1 | **364** (61%) | **34** (25%) |
| Rai 2 | **35** (6%) | **8** (22%) |
| Rai 3/4 | **45** (7%) | **18** (65%) |
| SLL | **81** (13%) | **10** (12%) |
| MBL | **47** (8%) | **2** (4%) |
| Unknown | **20** (4%) | **1** |
| ***Total*** | ***592** (100%)* | ***73** (post-CLL)* |

**Table 2.** Rai stage at the time of CLL diagnosis (all patients) and the first skin cancer diagnosis (patients with post-CLL skin cancer).

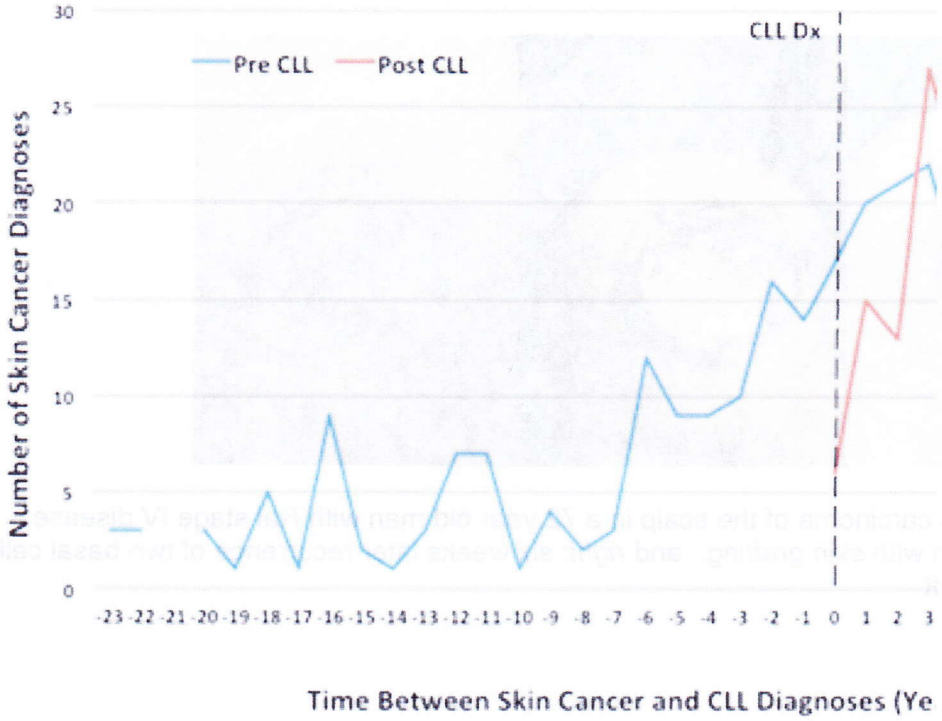


**Fig. 3.** Frequency of skin cancers in CLL patients

| Causes of Death | n | % |
|---|---|---|
| CLL | 47 | 35 |
| Skin | 3 | 1 |
| Other cancers | 22 | 17 |
| Non-Malignant | 24 | 18 |
| Unknown | 39 | 29 |
| *Total* | *135* | *100* |

**Table 3.** Causes of death in the CCMB Clinic cohort

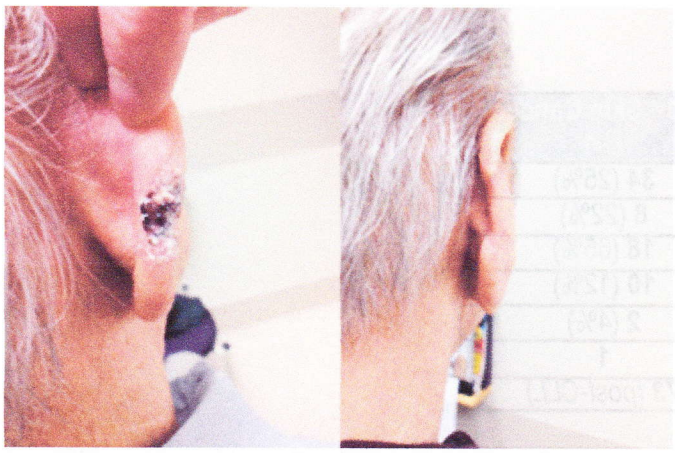

**Fig. 4.** *Left*: squamous cell carcinoma of the right ear in a 77 year old man with Rai stage 0 CLL, and *right*: following resection

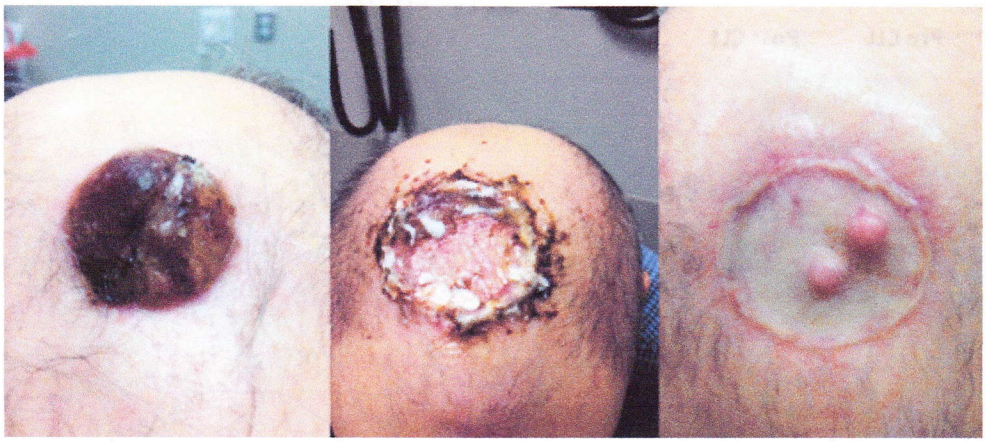

**Fig. 5.** *Left*: basal cell carcinoma of the scalp in a 72 year old man with Rai stage IV disease, *middle*: after resection with skin grafting, and *right*: six weeks later recurrence of two basal cell carcinomas in the graft