6. Extranodal Lymphomas

Prognostic factors and therapeutic efficacy of combined radiochemotherapy in Waldayer's ring non-Hodgkin lymphoma

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Introduction: Objective to improve the prognosis and therapeutic efficacy of Waldayer's ring non-Hodgkin lymphoma (NHLL-WR), combined radiochemotherapy was used to treat the patients with NHLL-WR and prognostic factors were analyzed.

Methods: 90 patients with stage I-IV NHL-WR were treated with combined radiochemotherapy 4000cGy to 6000cGy were given in Waldayer's ring structure and involved cervical nodes. Uninvolved low cervical nodes received 3000cGy to 4000cGy. The combination chemotherapy consisted of CVP (Cyclophosphamide [CTX], Vincristine [VCR], Procarbazine [PCZ]), Prednison (PDN) or CHOP (CTX, ADM, VCR and PDN). Univariate analysis was performed to determine the prognostic unfavorable factors.

Results: 5-year overall survival rate was 69.7% for the whole group, 83.2% for patients with stage I-II. In univariate analyses, CS rates of the patients with low and intermediate grade (76.1%), with stage I-II (83.2%), without fever (75.2%) and Performance status (PS) 0-1 (85.7%) were significantly better than those of the patients with high grade (53.0%), stage III-IV (24.7%) with PS2 (41.7%), PS 3-4 (0.0%), respectively (p=0.05 each).

In the past, non-Hodgkin lymphomas of Waldayer's ring (NHLL-WR) have been treated with radiotherapy alone. Progression is usually outside the irradiation fold. In order to improve therapeutic efficacy, we tried to treat the patients with NHL-WR with radio-chemotherapy. In this report, Combined radiochemotherapy improved 5-year survival rate for the patients with NHLL-WR, especially for stage I-II patients. PS2, stage III-IV, fewer and high grade histology were associated with unfavorable prognosis.

ADVANCES IN MANAGEMENT OF PRIMARY CNS LYMPHOMA

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Introduction: The historical association of acrodermatitis chronica atrophicans (ACA), now known to be a late manifestation of Lyme disease caused by Borrelia afzelii, with cutaneous lymphoma, and several small series of PCBCL with positive Lyme disease borrelial serology initiated a study of this association. In the last nine years, 30 patients with PCBCL have been observed and followed. 22 of these were tested for borrelial serology. The control group consisted of 60 patients with NHL. Both ACA patients were positive only on the screening tests, 2/3 with extra nodal NHL (localizations in nasol and oral cavity), and non were positive in the cutaneous T-cell, nodule B-cell NHL, breast cancer and blood donor group. Two patients with PCBCL were positive for B. afzelii, additional 3 on the Swiss strain WB, and 8 on the Bavarian strain WB; 2 patients were positive on both WB tests. Two patients were positive only on the screening tests, thus possibly false positives. Two positive patients had ACA, one arthritis. Both ACA patients were positive only on the Bayerian strain and not on the Swiss strain WB. In conclusion there appears to be a clear clustering of positive serology for lyme disease Borrelia in the PCBCL group possibly indicating an epidemiological relationship. Mechanisms of Borrelia escape from immunosurveillance mechanisms, persistence of these both mitogenic and antigenic stimuli for B-cells, and SALT formation may be involved in the pathogenesis of some PCBCL.

HIGH GRADE WALDHEYER'S RING LYMPHOMA: COMBINED CHEMO-AND RADIOTHERAPY

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Forty-two patients (pts) with high grade non-Hodgkin's lymphoma of Waldayer's ring (WR), stages I-IV, were treated by cheo (CT) and radiotherapy (RT) at the Kyrgyz Institute of Oncology during the period 1986 to 1997. Twenty-five pts were females and seventeen of them were males. The site of involvement within the WR lymphoma was tonsil 28 (66.7%), nasopharynx 11 (26.2%) and base of the tongue in 3 (7.1%) of the pts. The mean age was 43 years with range 16-68. These pts treated with 5-8 cycles CHOP and other anthracycline based CT and loco-regional RT (24-36 Gy).

Results: 15 pts (46.2%) achieved a complete remission, 8 pts (25.0%) - a partial remission (OR - 23/42 pts, 71.9%). The 5-years overall and relapse-free survival was given 57.4% and 42.9% respectively. These results and future therapeutic strategies will be discussed.
PRIMARY BONE LYMPHOMA: SINGLE CENTER EXPERIENCE
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Introduction: Primary bone lymphomas (PBL) are rare extranodal lymphomas accounting for 1% of all cases of non-Hodgkin's lymphomas. Optimal management of these tumours is unknown. We have retrospectively analysed our experience on this rare lymphoma type.

Patients: Between 1989-1999, altogether 12 patients (pts) with PBL were diagnosed and treated at our hospital. There were four women and eight men with a median age of 57 years (25-69 yrs).

Results: All lymphomas were of B-cell origin. Histopathological diagnoses included large cell (N=10) and follicular (N=2) lymphoma. Pelvis and vertebram were the most common sites involved at diagnosis (three pts each) followed by femur (two pts). Serum level of lactate dehydrogenase was elevated in six patients. The international prognostic index ranged from 0 to 3 (median 1). All patients were treated initially with CHOP or CHOP-like regimens (3-11 cycles, median 8 cycles). In addition, five patients received high-dose methotrexate (HD-Mtx) and six patients intrathecal methotrexate (I.t.Mtx). Local radiotherapy (36-40 Gy) was given to eleven patients. Autologous stem cell transplantation has been performed in two patients, in one patient as a consolidation therapy and in another as a salvage treatment after relapse in the spine. With a median follow-up of 41 months (5-104 months) all patients are alive. Two patients have relapsed but are now at 2nd and 3rd remissions 43 and 60 months from the diagnosis.

Conclusions: Anthracycline-based combination chemotherapy plus local radiotherapy seems to offer excellent survival in this patient population. HD-Mtx/I.t.Mtx may be useful to prevent central nervous system relapses.

IMAGING ALGORITHM FOR PRIMARY BONE LYMPHOMAS (PBL) AND REVIEW OF ELEVEN CASES
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Preface: According to Shoji and Miller criteria, eleven NHL cases were classified as primary bone lymphomas (PBL), and were under follow up since 1986 at our Institute.

Patients characteristics: three patients had truly localized (monostotic) disease, three patients had polyostotic disease and five patients monostotic disease accompanied with other localizations. The most frequent bone localization was femur (6 patients), and the common histological type was centroblastic (7 patients).

Algorithm: skeletal radiographs of involved region(s), then bone scintigraphy and in recent cases MRI of affected region(s).

Treatment: all of patients received chemotherapy as primary treatment. Concomitantly in three cases radiotherapy was performed.

Results: median follow up time was 14 months (range: 4-88 months). Five patients are in CR with duration 8, 14, 20, 28+ and 34+ months. One patient is in PR without change of final MRI presentation of bone disease after 13+ months. Two patients died with relapse/progression of disease after 8/16 months, and three patients are too recent for response evaluation.

Conclusions: initial radiographs showed different appearances of bone changes. In five cases we found typical osteolytic lesions, in two cases less typical osteoclastic lesions, in three cases mixed osteolytic/osteoclastic lesions and in one case "osteoplastic" lesion. On control radiographs, various degrees of sclerosis was seen. Initial MRI was performed in four recent cases with typical T1 hypot2 hypertense signals, with different degree of bone marrow remodulation on control MRI's.

MYCOSIS FUNGOIDES/SEZARY SYNDROME: THERAPY AND DILEMMA
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Introduction: Recombinant interleukins are active agents against MF/SS, with response rate of about 50% for patients with advanced disease, refractory to other treatments. Initial studies used extremely high doses, but similar response rates were found with lower doses. Recently it was demonstrated that even in initial stages of MF, the T cell clone is present in low amounts in the peripheral blood. Therapeutic systemic therapeutic modalities alone or in combination with local strategies should be more effective.

Objectives: to determine whether interleukins should be combined with other active agents such as etoposide, preferentially in the treatment of cutaneous tumors stage of MF and also in plaques forms progressive to standard topical/PUVa therapies and interleukins alone.

Patients and methods: During the past decade 12 cases of MF and 2 cases of SS were identified. Median age was 65 years and m/f ratio was 10/4. The pts were classified according to MFCCG proposals, with dominance of stage 1b, registered in 7 pts. In time of our hospital admission. All pts were previously treated. 7 with topical nitrogen-mustard and corticosteroids, 3 with PUVA and 4 with interferon-a2a. Interferon was given according to widely accepted criteria, mostly using continuous escalating dose.

Results: Median time to progression (TTP) to initial treatment was 48 months, range 6-144 m. In our institute, combination of etoposide in dose of 120mg/m²/day (1.3 and 5) and INF-a2a (day 1-15) as second line therapy, was conducted in all pts. with various number of cycles, range 1-32, average 10 cycles. Overall response rate was 6/14, with 3 complete remission and 3 partial remission. In 4 pts. we didn't achieve any response. Median TTP of secondary treatment was 14.5 months. Overall survival was 67.5 months, range 8-156 months. Toxicity was usual with no therapy related deaths, but in 2 pts. we registered leukemic transformation. Among long survivors we identified 3 second malignancies: adenocarcinoma recti, promyelocytic leukemia and cutaneous basal cell carcinoma.

Conclusion: The present study shows that cutaneous tumors and extracutaneous disease is very poor. Adding of etoposide to INF-a2a seems to give some benefit for this pts, but we need further studies to determine precise role of this combination in various stages of MF/SS.
GRANULOMATOUS SLACK SKIN: CLINICAL AND HISTOLOGIC FEATURES OF TWO PATIENTS WITH SKIN AND LYMPH NODE INVOLVEMENT

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Introduction: Granulomatous slack skin is a rare cutaneous T-cell lymphoma with characteristic clinical and pathologic findings, in which hanging folds of skin show a granulomatous histology. First described by Ackerman in 1970, only 30 cases have been reported in the literature. While considered by many an indolent form of cutaneous lymphoma, approximately one third of patients are reported to develop Hodgkin’s disease.

Methods: We reviewed the clinical course of two patients with GSS, both with skin and lymph node involvement. We performed polymerase chain reaction (PCR) amplification of genomic DNA and DNA sequencing on tissues obtained from the skin and lymph nodes of each patient.

Results: In both cases, the patients had the characteristic pendulous folds in the flexural areas. Their disease was resistant to a combination of anti-inflammatory and chemotherapeutic agents. One patient developed a secondary immunohistochemical visceral lymphoma which responded to CHOP, while his cutaneous GSS disease progressed. He eventually died from progressive nodal GSS disease. In both patients, the histopathological examination of skin biopsies revealed giant cell granulomas with destruction of the dermal elastic tissue, while the lymph nodes had similar giant cell granulomas. For each patient, we demonstrate by PCR, the presence of the same T-cell clone in the skin and lymph node.

Conclusions: GSS has characteristic clonal T-cell population in both skin and lymph node, consistent with its classification as a cutaneous lymphoma. While indolent in nature, patients may die of their disease or from a subsequent lymphoma.

6. Extralymphatic Lymphomas

ORBITAL AND ADENAL INVOLVEMENT IN ADVANCED NON-HODGKIN’S LYMPHOMAS

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Introduction: The aim of the work was to analyze the appearance of orbital and adenal lymphomas depending on development of extralymphatic lymphomas, to study their clinical symptoms and methods of treatment.

Methods: 20 patients (age from 14 to 74 years) suffering from advanced non-Hodgkin’s lymphoma (NHL) with orbital, lid or conjunctival tissues involvement were treated from 1989 through 1998. Male/female ratio was 2.3: NHL was diagnosed based on morphological investigation of peripheral lymph nodes (in 8 cases), extranodal NHL (in 12 cases including 6 biopsies of synchronous orbital and conjunctival tumors).

Results: Eye damages were distributed as follows: orbital NHL were noted in 13 cases, lid NHL in 2 and conjunctival NHL in 1 case. 3 patients revealed simultaneous infiltration in the upper lid and orbital tissues. After 9 mths, one patient with a bilateral orbital NHL developed NHL of the upper conjunctival fornix and left iris. 13 patients had unilateral NHL, while 7 patients showed bilateral orbital and adenal eye damage. According to REAL classification (1994), 18 NHL were of B phenotype. follicular (6), diffuse large-cell (4), mantle cell (4) and Burkitt’s-like NHL (2). Orbital and adenal NHL appeared simultaneously with extranodal NHL in 6 cases including 4 NHL of soft tissues and one patient with damaged peripheral lymph nodes. In 11 cases with preceding extranodal NHL, orbital tumors appeared after 12-60 mths (median 24 mths). The following extranodal tumors were registered: lymph node NHL (7), gastric and intestinal NHL (2), NHL of Valdezas’ ring (2), NHL of soft tissues (1) and breast (1). In one patient, right orbital mantle NHL metastasized in neck lymph nodes after 60 mths; no treatment was provided before generalization of tumor process. Adequate chemotheraphy (COP, LVPF) was efficient in treatment of NHL of other organs while being inefficient in treatment of orbital and adenal low grade NHL. In 45% such patients, complete remission (CR) was achieved only after local irradiation of the orbit. Duration of CR was 6-72 mths (median 24 mths). In patients with high grade NHL, CHOP-like regimes were efficient in 3 out of 4 patients, only in one patient CR was achieved after additional local irradiation of the orbit. Duration of CR was 9-24 mths (median 18 mths).

Conclusions: Orbital and adenal damages appeared simultaneously with extranodal NHL or followed them. Only one patient revealed advanced orbital NHL. Discordant effects were noted in thymus of advanced NHL; sensitivity of extranodal NHL had no correlation with sensitivity of orbital and adenal NHL; efficacy of chemotherapy was significantly lower in low grade NHL than in high grade NHL.

REMISSION OF PROTEIN-LOSSLING GASTROENTEROPATHY FOLLOWING CHEMOTHERAPY IN A CASE OF NON-HODGKIN’S LYMPHOMA.

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Protein-losing gastroenteropathy (PLGE) may contribute to hypoalbuminemia in patients with cancers of digestive tract. Occasionally, cases of Hodgkin’s and non-Hodgkin’s lymphoma with PLGE have been reported. In the latter PLGE may be due to the lymphoma involvement of digestive mucosa or may appear as paraneoplastic syndrome, possibly due to lymphatic obstruction. However, some doubts have been raised on the last possibility. We report a patient with non-Hodgkin’s lymphoma and PLGE without evidence of lymphoma localization in the digestive tract and who has shown signs of recovery following chemotherapy. A 63-year-old caucasian male was admitted with a four week history of ankle edema which was attributed to hypoalbuminemia (total protein 36 g/L, albuminemia 24.2 g/L, globuln 11.8 g/L). Protein-losing nephropathy, liver disease or malnutrition were excluded and hypoproteinemia was attributed to PLGE. Splenomegaly and lymphocytosis prompted further diagnostic work-up which revealed a non-Hodgkin’s lymphoma B-CLL type (CD 19++, CD 51++, CD 20++, CD 22++, CD 23++, HLA DR++, normal karyotype). No significant peripherical lymph nodes were detected, but abdominal CT revealed involvement of peri gastric, pericardial, pericolic, mesenteric, paracolic, paracaval and hepatic hilar lymph nodes. Gastroduodenal endoscopy (performed twice) showed a diffuse moderate thickening of gastric folds with scattered zones of hyperemia. Endoscopic biopsies showed foveolar hyperplasia, edema and laminae propria neutrophilic infiltration. Neither these biopsies, nor radiological images, gave evidence of lymphoma localization on the digestive tract. Fluoradarine (25 mg/mg x 5 d) treatment was begun. Following the third course of therapy lymphoma signs partially regressed and total protein reached 54 g/L, albuminemia 33.8 g/L, globulin 20.2 g/L.
NON-HODGKIN-LYMPHOMAS OF BONE: A LONG TERM FOLLOW UP.
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We present a retrospective study of 19 patients with primary non-Hodgkin-Lymphomas of bone (NHL-B) treated and followed for 1-201 months (median 94 months). 19 patients with NHL-B were identified, histologically reviewed and treated by our institutions from 1982-1988. The NHL-B was located in the thigh (9x), in the pelvis (6x), others included spine, clavicula and humerus. The initial symptoms were pain and palpable tumors, but rarely B-symptoms or hypercalcemia. Osteolytic bone changes were mostly seen, one patient presented with sclerotic changes only, a mixed pattern was identified as well. 11 patients presented solitary lesions confined to one bone, the others had several bony lesions. According to Ann Arbor Classification 10 patients were IE (1 extra nodal manifestation) and 9 stage IV disease, 2 were IVF-F, 12 IVF-G and 5 IVF-H. After diagnostic biopsy, 18/19 underwent a CHOP-like chemotherapy, followed by involved bone radiation in 13 patients. 2 patients underwent high dose chemotherapy and bone marrow retransfusion due to unfavourable risk factors, one is too early for response assessment. Treatment responses included 1 CR (histologically confirmed) and PR in 8/10 patients assessable because of soft tissue masses adjacent to the bone involved. 2 patients had progressive disease, underwent salvage treatment and died of progressive lung and CNS disease respectively after 5 and 6 months. 18/18 patients with completed therapy (89%) are alive and free of disease after a median observation time of 94 months (range 7-201 months).

Response assessment is difficult, 1 patient had a biopsy proven complete remission, 14 patients had remaining bone changes after completion of multimodal treatment that included diminishing osteolytic areas and increasing sclerotic changes. Bone remodelling was observed in sacral, humeral and pelvic NHL-B, it was a slow process and occurred gradually over 4-7 years. In summary we confirm the experience of others, that standard therapy of NHL-B includes chemotherapy and local radiation.

SOLITARY PLASMACYTOMA TREATED WITH RADIOTHERAPY: IMPACT OF TUMOUR SIZE ON OUTCOME
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Introduction: Solitary plasmacytoma (SP) is a rare presentation of plasma cell dyscrasias (~6%). Long-term disease-free survival is possible following local radiotherapy (~), particularly for non-osseous presentations. We wished to identify factors that predict for local failure, progression to multiple myeloma (MM) and survival in patients (pts) mainly managed with local RT. Methods: A review of 46 pts from years 1982-93 was performed. The median age was 63y (range 35-85y), with M:F ratio 1:9.1. All pts had biopsy proven SP (osseous: 32, non-osseous: 14) with normal bone marrow and skeletal survey. M-protein was abnormal in 19 pts (41%). All pts were treated with local RT (median dose: 35 Gy), with 5 pts (11%) receiving additional systemic chemotherapy. Maximum tumour size pre-RT ranged from 0.1-18 cm (median 2.5 cm).

Results: After a median follow-up of 7.9 years, the 8-year disease-free survival (DFS) and myeloma-free rates were 44% and 50% respectively. There were 7 pts with local failure (8-y local control rate: 83%). Factors predictive of progression to myeloma (and hence DFS) included osseous site and older age (see Table). In contrast, these two factors did not influence local control, which was predicted by tumour size. All tumours <5 cm in bulk (34 pts) were controlled by RT. Anatomic location did not predict outcome, except that 3 of the 5 tumours arising in paranasal sinuses did not achieve local control. None of RT was not associated with local failure.

Conclusions: Solitary plasmacytomas are effectively treated with moderate-dose RT, although osseous tumours have a high rate of recurrence as systemic myeloma. Large tumour bulk locally (>5 cm) predicts for local failure. Combined chemotherapy and RT needs to be investigated in these high risk patients to increase the cure.

NONGASTROINTESTINAL LOW-GRADE MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT) LYMPHOMA: ANALYSIS OF 75 PATIENTS
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Introduction: Nongastrointestinal locations represent about 30-40% of all low-grade MALT lymphomas. We report a retrospective analysis of 75 patients with nongastrointestinal low-grade MALT lymphoma, presenting their clinical, therapeutic and follow-up data with respect to the initial location of the lymphoma.

Methods: From January 1988 to October 1997, 75 patients with untreated nongastrointestinal low-grade MALT lymphoma were submitted to treatments ranging from the local approach of radiotherapy and local α-interferon (α-IFN) administration to chemotherapy. The lymphomas were located in the lung (19 patients), orbital soft tissue (16 patients), skin (7 patients), lacrimal gland (6 patients), conjunctiva (6 patients), salivary gland (6 patients), breast (3 patients), eyelid (2 patients), larynx (1 patient), bone marrow (1 patient), and trachea (1 patient).

Results: Complete and partial remissions were achieved in 59/75 (79%) and 16/75 (21%) patients, respectively, with an overall response rate of 100%. All but two of the patients are still alive with a median follow-up of 47 months; these 2 patients died from other causes. The estimated time to treatment failure rate is 30% at 5 years. In the thyroid and lacrimal gland locations no relapses were reported.

Conclusions: Our data regarding the largest reported series of nongastrointestinal MALT lymphomas confirm the good prognosis of this particular clinicopathologic entity and the significant efficacy of different therapeutic approaches to specific sites.
LARGE T-CELL MYOCYTOMY IN FONGOIDES

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The course of Mycosis Fungoides (MF) is usually indolent for many years, but transformation in large T-cell lymphoma (defined by more than 25% of large cells among the tumoral infiltrate) may occur as a late event of poor prognosis. Our purpose was to determine the clinical and prognostic value of clinicopathological features of transformed MF. We have selected the cases of the 44 patients with histological transformation of MF from the files of the French Study Group of Cutaneous Lymphomas. Their main clinical characteristics were studied. Cutaneous biopsies were analyzed and studied by immunohistochemistry with the following antibodies: anti-CD3, CDS, CD4, CD8, CD20, CD68, CD30, CD5, MIB1.

The time between first cutaneous lesions and transformation (mean 14 years) and between the diagnosis of MF and transformation (mean 6 years) were not predictive for the survival. After transformation, 12 deaths due to lymphoma occurred in a period of 23.5 months (42% of survival after 36 months) that is similar to the prognosis of primary pleomorphic large-cell lymphoma. The principal prognostic factor was the extent of extracutaneous spreading (p < 0.03). Lymph nodes were frequently involved in 2 patients, but they corresponded to CD30+ lymphoproliferations associated to MF, that need a different management and have to be distinguished to transformed MF according to its clinical features, since histology may be not discriminative. In 4 patients, the histological transformation was present on an previous biopsy while no clinical transformation was observed. In tumors with large cells, the relative number of large T-cell was up to 50%. They were frequently mixed with B-cells, that may make difficult the diagnosis. The large cells were CD4+ and in most of them CD30+. The expression of the oncokroyteki CD30 and S100 was not significantly different between MF and transformation. Lastly, for inclusion, we used the CD68 immunostaining to rule out granulomatous MF which is an important differential diagnosis. It is necessary to make earlier the diagnosis of transformed MF, with regular systematic biopsies, since histological transformation may precede clinical transformation. However the impact on survival of an earlier diagnosis must be confirmed on prospective studies.

Natural history of low grade gastric MALTI lymphoma: A single Institution evaluation.

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The aim of the study was to evaluate the role of histology and molecular analysis, of gastric polymorphic chain reaction (PCR), on the diagnosis and follow-up of low grade mucosa-associated lymphoid tissue (MALT) lymphoma and the effect of eradicating Helicobacter (H pylori) infection on the course of the disease. Sixty two patients with a diagnosis of early MALT lymphoma were included in the study. H pylori infection was documented in 57 out of 62 cases. Histologically, the patients were classified as belonging to Wohrer's grade 4 (n: 39) or grade 5 (n: 23). Immunoglobulin JH gene rearrangement using FR2 and FR3A primers by PCR analysis demonstrated the presence of a B clonal population in 59 out of 62 cases (95.1%). Eradication of H pylori was obtained in 40 out of 57 cases (70.1%) using a combination of amoxycillin plus clarithromycin and omeprazole for one week. Patients without evidence of H pylori infection (n: 5) were treated with claromucril. For 52 patients, a mean follow-up of 19.6 months was available, and a gastroscopy with multiple biopsies was performed every 3-6 months. Histological regression, i.e. Wohrer's grade 1 and 2 score, was documented in 47/52 cases (90.3%) and PCR evidence of clonality disappeared in 35/44 cases (79.5%). In a subset of 11 cases, a mean follow-up of 42.5 months was available. H pylori infection was eradicated in all these cases and histological and molecular regressions of lymphoma were demonstrated in 9/11 (81.8%). Taken together, our data demonstrate that a relevant percentage of low grade gastric MALT lymphomas could completely regress after H pylori eradication, without evidence of lymphoma relapse during the follow up.

SUBCUTANEOUS NK/T CELL LYMPHOMA

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Introduction: NK/T cell lymphoma in the nasal region shows the characteristics of an anergic pattern in histology, expression of CD56 and TIA-1, silent TCR and strong relation to EBV. However, it has been also reported that cases of NK/T cell lymphoma reflected in a case of secondary disease free survival, similar to MALT lymphomas, is not clear. We compared population based data of WR NHL, nodal NHL and gastric MALT NHL patients to answer this question.

Material and methods: We examined 15 cases of subcutaneous lymphoma with expression of CD56 or TIA-1. Phenotypes and cell lineage were determined by immunohistochemistry and Southern blotting. EBV was examined by INB, Southern blotting with the TR probe, and PCR.

Results: We recognized that there were three groups of subcutaneous lymphoma according to the pattern of CD56 expression and TCR rearrangement; 1, NK cell type (CD56+ and TCR silent); 2, NK like T (CD56+ T cell type, 3, T cell type (CD68- and TCR rearranged), although we were not able to divide them into three groups only by the histology and distribution of lymphoma cells. The NK cell type (6 cases, 1 male and 5 females, median 57 yrs) was similar to nasal NK/T cell lymphoma, with usual pleomorphic histology, absence of CD5, TCR, or CD3 expression and the high prevalence of clonal EBV infection. All patients died within 28 months. The NK like T cell type (5 cases, 5 females, median 66 yrs) included anaplastic large cell lymphoma with expression of CD30 in 2 patients, anaplastic large cell lymphoma with expression of CD30 in 2 patients, and anaplastic large cell lymphoma in 1 patient. There was no case with EBV infection. Three patients were deceased. T cell type (4 cases, 1 male and 3 females, median 57 yrs) showed the expression of CD3, CD5, and TCDR. Three cases had pleomorphic and one centroblastic type. One of pleomorphic type revealed the clonality of EBV. All patients are alive.

Conclusion: NK type is identical to nasal type NK/T cell lymphoma. NK like T cell type included histologically large cell lymphoma and its entity remains unclear. T cell type is compatible with subcutaneous plasmatic-like T cell lymphoma, although one patient presented clonal EBV infection. The patients in this type are younger than other two groups and carry good prognosis.

6. Extramedullary Lymphomas
Stomach lymphoma: The Scotland & Newcastle Lymphoma Group Experience.

The SNLG has collected prospective data on all cases of gastro-intestinal lymphoma presenting in their population of 8 million people during a three year period 1994-96. Over 360 were registered. 329 were included in the study after inspection of patient records and/or histopathology reports. 163 of the 329 (49.5%) were lymphomas of the stomach. There were 90M and 73F with a median age of 68. Cases came from 49 different hospitals with 31 hospitals seeing an average of 1 patient/year. Major presenting features were abdominal pain (85%), nausea and vomiting (54%) and weight loss (28%). Only 11% of patients had a palpable abdominal mass at presentation and only three patients (2.7%) presented with perforation of the stomach. B symptoms (excluding weight loss) were uncommon (<10% patients).

Analysis of histology at presentation revealed the majority of patients to have high grade tumours (62.5%) with 37 of 102 (36%) showing features of malignta. By contrast, 31 patients had low grade tumours, 27 of whom had low grade malormas. 3 patients had mantle cell lymphoma. The presence or absence of helicobacter infection was not uniformly reported by histopathologists. The organism was definitely present in 37 patients, definitely absent in 19 and presence or absence not noted in the remaining patients. Other tests for helicobacter infection were not uniformly recorded in the case notes.

Staging of disease was by the Burchell method (1). Ten patients had no staging investigations, 43 were stage I, 41 were stage II, 20 stage III and 19 stage IV. Staging information is awaited in 30.

Standard treatment protocols were not available. Treatment has been coded according to each modality used. Survival data will be presented by histology, stage and treatment code.


Gastric lymphoma: Evolution of treatment approach during three decades. Experience of North-Israel Oncology Center.
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Introduction: In the last three decades a number of developments have changed the management of primary gastric lymphoma (PGL): 1. endoscopic biopsy, CT scan and endoscopic ultrasonography enable a full diagnostic evaluation in almost cases. 2. Increasingly effective chemotherapy using multiple drug combinations has become available. Thus, the management of PGL has evolved to the era of multimodality therapy and effort of stomach conservation. We retrospectively analyzed the impact of surgery and radiotherapy on the outcome in respect of the highly effective chemotherapy, in our experience with PGL.

Patients and methods: During the years 1968 - 1995, 93 patients with PGL were referred to our center. Most (67%) had intermediate or high grade lymphomas and the other had low grade or MALT lymphomas. Histological diagnosis was established by endoscopic biopsy in 70% of the patients and by laproscopy in 30% of pts. Fifty eight (63%) had localized disease (stage I, II, III). Radical or partial resection was performed in half of the pts. Chemotherapy was given to 72 (77%) pts. Radiotherapy was given, usually post-operation or post-chemotherapy, to 35/93 (36%) of pts.

Results: CR was achieved in 73/93 (78%) of pts. Nine (12%) of them had a relapse, usually, in extra-nodal sites. Gastric recurrence was seen in only one pt who had initially bulky > 10 cm) disease. Overall survival for 5 and 10 years was 80% and 73%, respectively. Pts with localized disease treated either by surgical resection or by chemotherapy and conservation of the stomach had no difference in the 10 years survival. 81% and 86% respectively. Three pts, conservatively treated, developed gastro-intestinal bleeding, however, they didn't require surgery.

Conclusions: 1. Stomach conservation may be obtained in most pts with localized PGL. 2. Surgery would be reserved for those with poor prognostic factors: i.e.: non-responders or those with bulky tumor. 3. The role of radiotherapy is not clear and it should be investigated in further prospective studies.

6. Extraneous Lymphomas
HIGH GRADE B-CELL LYMPHOMA OF MUCOSA-ASSOCIATED LYMPHOID TISSUE
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Introduction: Mucosa associated lymphoid tissue (MALT) lymphomas are indolent neoplasms which tend to remain localized for a long time before sprouting. Transformation to a large cell (high grade) Hodgkin lymphoma can occur.

Methods: Eleven patients with HG MALT lymphomas (18% of all MALT NHL in the last 2 years) were reviewed. The series was comprised of 7 females and 4 males, mean age 55 years, ranged from 42 to 68. We histologically characterized tumors as HG MALT NHL in cases where more than 30% of tumor tissue was composed of large cells in the presence of low grade (LG) component and lymphoplasmacytic lesions. Besides details immunophenotypic analysis with monoclonal antibodies (CD20, CD79a, IgM, CD3, CD30, CD102, CD21, CD1c) ancillary investigations with PCNA, Ki-67, p53 and bcl-2 were performed in all cases.

Results: Nine cases were initially diagnosed as HG MALT NHL. The bone marrow was infiltrated in 33% pts at presentation. Tumors were localized in: stomach (3), all 6 involved pylori +, salivary glands (2, one associated with AIDs), biliary mucosa (1), small intestine (1), uterus and cervix (1), and testis (1). In two pts, initially diagnosed as LG MALT NHL, HG transformation appeared 6 months and 4 years later. First pt was 51 years old female with LG MALT NHL of the stomach. In the initial biopsy, small focus of large cells was noticed beneath the serosa. Six months later multiple nodules appeared in submucous tissue and both breasts, morphologically composed exclusively of the large cells. Other pt, 41 years old male, initially (1994) had multicentric LG MALT NHL in esophagus, stomach and small intestine. First LG relapse (1996) occurred in lymph nodes, skin and omentum, second (1996) in oesophagus and ileocecal valve. The last relapse, this time of HG morphology, occurred in liver, gallbladder and left kidney. All analyzed tumors expressed characteristic immunophenotype (CD20+, CD79a+, surface IgM, CD43 and CD1c+ positive in the minority of cells and CD5, CD10, CD21 negative). Growth fraction measured by PCNA and Ki-67 was high in all HG tumors. All tumors strongly expressed p53. The majority of tumor cells were negative for bcl-2.

Conclusions: HG MALT lymphoma is now well established entity. Besides morphological parameters and immunophenotype, parameters of cell kinetic must be used to separate between low and high grade MALT lymphomas.

TREATMENT OF PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA IN IMMUNOCOMPETENT PATIENTS
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Purpose: The purpose of the study was to evaluate the response to treatment and survival of immunocompetent patients with PCNSL. We retrospectively analyzed the data of 62 patients treated at the Department of Neurology and Neurosurgery, Charles University Hospital, Prague, Czech Republic.

Methods: The study included 62 patients with biopsy-proven PCNSL. The median age was 62 years (range 19-92). The diagnosis was confirmed by biopsy, and all patients received chemotherapy. The treatment regimens were based on the International Extranodal Lymphoma Study Group (IELSG) guidelines.

Results: The overall response rate to treatment was 79%. The median survival time for all patients was 36 months. The 5-year survival rate was 48%. The most common side effects were neurotoxicity and hematological toxicity.

Conclusions: Our results indicate that intensive chemotherapy, including rituximab, can effectively treat PCNSL in immunocompetent patients. Further studies are needed to evaluate the long-term outcomes and the role of maintenance therapy.
IMPACT OF MOLECULAR BIOLOGY IN CTCL DIAGNOSIS

Introduction: The diagnosis of typical forms of mycosis fungoides (MF) or other CTCL is performed, in most of the cases, by means of the experience of the clinician and then confirmed by histological and immunophenotypical examination. Moreover suspected cutaneous lymphoproliferative disorders might be analysed by a PCR technique: DNA samples are extracted from lesional skin or peripheral blood lymphocytes (pbl). In our experience there are patients suffering from a suspected T-lymphoproliferative disorders in which the traditional investigations are not able to provide a reliable diagnosis. In these cases the molecular biology investigation may become an invaluable tool for the diagnosis. In this study we will review the cases in which this event has occurred.

Methods: 104 patients were examined by histological, immunophenotypical and molecular analysis. PCR was performed in all cases on the DNA extracted from frozen lesional skin; in 18 cases the same investigation was repeated on pbl.

Results: Molecular data (clonality) strongly supported the diagnosis of CTCL in the following cases: 5 cases of follicular mycosis fungoides, 12 cases of erythrodermic mycosis fungoides or Sézary syndrome (in 6 of them pbl showed the same rearrangement), in 2 out of 5 patients affected from lymphomatoid papulosis, in 6 subcutaneous panniculitis-like T-lymphomas and in 6 CD8+ MF-like T-lymphomas.

The absence of gene rearrangement resulted in several cases of parapsoriasis and, moreover, 6 patients affected by CD56+ lymphomas, indicating a NK or a myeloid origin.

Conclusions: We believe that the spread of the molecular analysis is useful in dermatological and clinical practice, not only for the better understanding of the pathogenic mechanisms behind cutaneous lymphoproliferative disorders, but even to better define new clinico-pathologic CTCL entities.

PANNICULITIS-LIKE SUBCUTANEOUS T-CELL LYMPHOMAS: A CLINICO-PATHOLOGICAL STUDY OF SEVEN CASES

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The panniculitis-like subcutaneous lymphomas is a recently identified aggressive primary cutaneous cytotoxic lymphoma originating from T or v-lymphocytes. We describe the complete clinico-pathologic data of 8 patients (two children and 6 adults) affected from subcutaneous panniculitis-like T-cell lymphomas. These cases were observed in our department during the last 7 years. Five out of 8 cases died for dissemination of the disease in a medium time of 26 months. Two patients died for sepsis, three for pancreocarcinoma. Two adult patients are living in complete remission after polychemotherapy, respectively after 2 and 4 years of follow-up. The last case, a woman 32 years old, was recently observed and is in partial remission with lymaglia prednisono. Clinically four patients presented with disseminated subcutaneous non-inflammatory lipomatous-like nodules, whereas the other four patients cutaneous lesions showed variable degree of inflammation with erythema, burning and frequent ulcerations. All patients presented general symptoms at presentation and variable alteration of the peripheral blood with elevation of the ESR. In two cases we observed a myeloblastic syndrome with chromosome 8 trisomy in one. Histologically the patients showed the typical involvement of the subcutaneous fat with an interlobular and perifollicular internal and external lymphoproliferative high dermocystically lymphoid cells, sometimes showing cytologic atypia. Histocytes were numerous and show variable degree of erythroleukocytogranulosis and a granulomatous reaction. An angiocentric subcutaneous lymphoid infiltrate was also evident in most cases. However, in the four cases clinically showing an inflammatory evolution, we observed a strong granulomatous reaction in the adipose tissue and the perivascular angiocentric infiltrate also involved the mid and superficial dermis. The immunophenotypic studies showed that the infiltrate was formed in all cases from T-lymphocytes CD3+, TIA-1+ and TCR-alpha/beta+. 5 cases were CD8+. Molecular studies showed a clonal T-cell infiltrate in 7 out of 8 cases. Our study confirms previous reports, showing an aggressive clinical course for these lymphomas in most cases.

6. Extranodal Lymphomas

EXPRESSING OF CYTOTOXIC PROTEINS BY NEOPLASTIC CELLS IN MYCOSIS FUNGOIDES INCREASES WITH PROGRESSION FROM PLASQUE STAGE TO TUR STAGE: HISTOLOGY AND BIOPSY

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Introduction: Granulysine B (GB) and T-cell-restricted intracellular antigen (TIA-1) are cytotoxic proteins that are specifically expressed by cytotoxic T-cells and natural killer cells. Recent studies demonstrated expression of GB and TIA-1 by neoplastic cells in non-Hodgkin lymphomas including primary cutaneous CD30-positive large T-cell lymphoma and lymphomas with secondary CD30 expression. Expression of GB and TIA-1 in mycosis fungoides (MF) was not investigated thus far.

Methods: In the present study 74 biopsies from 54 MF patients were investigated for the expression of GB and TIA-1 using immunohistochemistry on perflavin sections. Staining of more than 10% of the neoplastic T-cells for GB or TIA-1 was considered positive. All but two follow-up biopsies had been obtained from patients without extracutaneous disease at the time of biopsy.

Results: Expression of TIA-1 and GB was found in 33 (65%) and 14 (19%) of 74 MF biopsies. Comparison of biopsies from T3N0M0 stage MF (n=27) and T2N0M0 stage MF (n=45) showed increased expression of TIA-1 (35% vs 37%) and GB (33% vs 5%) in T3N0M0 stage MF. A clearcut relation between the expression of TIA-1 and/or GB and the type of skin lesion biopsied was found. Considering all 74 biopsies, expression of TIA-1 and GB was found in 18/50 (35%) and 5/50 (10%) from plaques or plaques, 9/16 (55%) and 3/16 (20%) tumors with blastic transformation, 5/16 (31%) and 5/16 (31%) tumors with blastic transformation (defined as >50% blast cells). Correlation between GB/TIA-1 expression in first diagnostic biopsies from plaques or plaques from 40 patients with T2N0M0 stage MF and clinical follow-up data did not reveal differences in expression of cytotoxic proteins. Indicating that MB expressing cytotoxic proteins should not be considered as a separate group.

Conclusion: Neoplastic T-cells in MF can express cytotoxic proteins TIA-1 and GB and the expression of cytotoxic proteins increases with progression from plaque to tumor stage of disease.
TRIMETREXATE IN RELAPSED CUTANEOUS T-CELL LYMPHOMA.
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Introduction: Methotrexate (MTX) is the most active single agent in CTCL, but needs facilitated diffusion to enter cells, and polyglutamation to inhibit dihydrofolate reductase. Since transport or polyglutamation mutations may be associated with MTX resistance, and since trimetrexate (TMTX) enters cells by diffusion and does not need polyglutamation for inhibition, we decided to determine its activity in relapsed CTCL. Methods: Eligible patients (pts) had histologically confirmed CTCL, age ≥ 16 years, no HIV to other serious infections, no CNS disease, normal renal function, and > 1 prior systemic regimen. All pts signed informed consent, and were treated with TMTX (200 mg/m² IV Pd q14 days) without Leucovorin rescue. Responses received up to 12 injections, with dose adjustment for toxicity. Results: Of the 17 registered pts, 14 are evaluable, and are the subject of this report. Median age was 59 years (range 45-87), and 9 were male. According to REAL classification, 2 pts had Anaplastic Large Cell Lymphoma, 11 mycosis fungoides (MF) or Sézary Syndrome (SS), and 1 Peripheral T-cell Lymphoma. Transformation to large cell lymphoma was documented in 10/11 (91%) pts w/ MF/SS. Serum LDH was high in 4/14, V2-microglobulin > 3.0 mg/L in 4/11, and HTLV-I was detected in 1/14 pt w/ MF. Median number of prior regimens was 5 (range 2-15), and 5 pts had received prior MTX. Refractory disease (NR or PD) to initial therapy was present in 10/14 pts. During the regimen immediately preceding TMTX 10/14 pts had NR or PD. Response to TMTX included CR in 1, and PR in 8 of 14 evaluable pts. The overall response rate was 62% (95% confidence intervals 35%-89%). Responses were seen in 2/5 pts who had previously received MTX. For the 53 administered TMTX cycles, grade 3/4 toxicity included maculosis in 4%, infection in 14%, neutropenic fever in 10%, neutrophils <1.0K or 0.1K in 36% or 6% respectively, and platelets < 100K or 20K in 42% or 6%, respectively. Conclusions: TMTX has significant activity, with acceptable toxicity, in this very unfavorable population with relapsed CTCL. The study is continuing for better determination of response in less refractory patients, and in those previously treated with MTX.

HEPATOPLENILE Tp-NON HODGKIN'S LYMPHOMA SUCCESSFULLY TREATED WITH PBSC TRANSPLANTATION
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Introduction: Hepatosplenile Tp-NHL is a recently described entity with some decades of patients being published up to now.
Case report: A 32 years old patient was referred for evaluation of hepatosplenomegaly. He had noticed a left abdominal discomfort during the last 2-3 weeks. On physical examination a generalized lymphadenopathy with small lymph nodes, a palpable liver 3-4 cm and a spleen 5 cm below costal margins were noted. Hb was 12.8 g/dl, WBC 16000/mm³ with 29% neutrophils, 62% lymphocytes, some with atypical morphology and 9% eosinophils. Platelets were 64000/mm³ and ESFR 5 mm. Biochemical profile including liver enzymes, albumin, LDH, serum protein electrophoresis, immuno globulins and β2-microglobulin, was normal. Blood serology including antibodies for HBV, HCV, EBV, CMV, HIV and all autoantibodies gave negative results. On U/S and CT scan, liver and spleen were homogeneously enlarged (spleen size 23x12x16 cm) without internal lymphadenopathy. Bone marrow was infiltrated by CD2+, CD3+ lymphoid cells with clear cytoplasm, in an angiocentric, intrasinusoidal distribution. The patient underwent splenectomy with liver biopsy, which confirmed the diagnosis of N.H. lymphoma. Lymphomatous cells were CD2+, CD3+, CD4+, CD8+, CD5-, CD56+, CD57-, CD19-, CD20- and CD22-. In situ PCR analysis of spleen sections revealed the presence of clonal rearrangement in δ-chain gene region of T-cell antigen receptor. After splenectomy he was treated with the same cycles of the m-BACOD regimen and was consolidated with BEAM plus autologous PBPC support. Repeated immunophenotype and PCR analysis of peripheral blood, bone marrow and liver biopsy sections, no longer detected Tp-lymphocytes. Eighteen months after ABST the patient remains in complete remission and in excellent general condition.

MALIGNANT LYMPHOMAS OF THE NASAL CAVITY AND PARANASAL SINUSES
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Introduction: Malignant lymphomas arising in the nasal cavity and paranasal sinuses are unusual. A relatively high incidence of sinonasal lymphoma has been observed in Asian countries. We report our experience with 10 Japanese patients with primary sinonasal lymphoma. In particular, we describe three cases of nasal lymphoma characterized by natural killer (NK) cells.

Material and methods: We encountered 45 cases of malignant lymphoma in the head and neck region over the past 21 years at the Department of Otorhinolaryngology of Kawasaki Medical School Hospital. Of these 45 cases, 10 lymphomas arose in the nasal cavity and paranasal sinuses. Diagnostic biopsies examined and were stained with hematoxylin and eosin-stain in every case. Immunohistochemical studies, Southern blot hybridization studies, EBV-encoded RNA in situ hybridization studies and flow cytometry were performed in several cases.

Results: This study group consisted of six men and four women, ranging in age from 32 to 79 years old (mean, 60.2 years). The presenting symptoms included nasal stuffiness, epistaxis, swelling of the face, swelling of the eyelid and diplopia. The lymphomas arose from the nasal cavity in seven cases and from the ethmoid sinus in three cases. In immunohistochemical studies, two cases were considered to be T-cell lymphoma and three cases were considered to be B-cell lymphoma. None of these cases were undetermined. Eight patients received one to six courses of chemotherapy, THF-COP, ESHAP, CHOP, VEMP, EPOCH, Epi-CHOP. Six patients received local radiation therapy to a total dose of at least 40 Gy. Three patients had no relapse and were free of disease between 11 months and 97 months after diagnosis. Seven patients died of their tumor within 6 months after diagnosis. Conclusions: We encountered 10 cases of malignant lymphoma in the nasal cavity and paranasal sinuses. Three of 10 cases were very rare lymphomas derived from natural killer (NK) cells.

TESTICULAR LYMPHOMAS: A CLINICO-PATHOLOGICAL REVIEW OF 57 PATIENTS
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We have reviewed all patients with testicular lymphomas managed at the Christie Hospital since 1980 in order to characterise the clinical and pathological features further. Testicular lymphomas are an uncommon form of extranodal lymphoma which often carry a dire prognosis. A total of 57 patients (pts) who had had histology confirmed were reviewed. In 54 of 57 pts the diagnosis was made following an orchidectomy (25pts - left; 28 pts - right); the spermatic cord was involved in 13 of 35 pts (37%) who had had this examined. 53 of 57 pts (93%) had a high grade histology. The median age at diagnosis was 68 years (range 31-84 years). The clinical stages were: 1AE (28%), 1BE (2%), 2AE (8%), 2BE (2%), 2BEX (1%), 4A (10%), 4AX (1%), 4B (3%), 4BX (2%); 54 pts (95%) were judged not to have disease built. The median Karnofsky's PS was 90; mean LDH was 380 IU/dl (normal 240-480). 16 pts received XRT alone and 29 pts received chemotherapy (19pts VAP/EC-1; 1 pt CHOP; 1 pt ACP; 8 pts 'other'); 12 pts received no further therapy. The overall responses were available on 43 of 45 pts who received XRT or chemotherapy: 26 of 43 pts (61%) CRs, 4 of 43 pts (9%) PRs; 9 of 43 pts (21%) PD and 4 of 43 pts (9%) died on treatment. At the time of this analysis, 18 of the original cohort (32%) are alive; 25 pts (44%) have died from progressive disease. 3 pts (5%) died from treatment related causes and a further 2 pts (3.5%) died from a second malignancy; 9 pts (16%) died from other causes.
RADIOThERAPY FOR PRIMARY ORBITAL LYMPHOMA. A SINGLE INSTITUTION EXPERIENCE ON 18 PATIENTS.
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Purpose: The aim of this report was to analyze disease control, radiation-related complications and the rate of systemic disease progression in pts with primary orbital lymphoma treated with radiotherapy alone.

Methods: From October 1986 to May 1998, 18 pts with stage I primary orbital lymphoma underwent radiotherapy treatment at the Dept. of Radiotherapy and Nuclear Medicine of Padua. Clinical staging procedures consisted of history, physical examination, routine laboratory tests, chest X ray, total body CT scan (including the orbit) and bone marrow biopsy. They were 8 males and 10 females, median age 54.5 yrs (range 26-84). The disease involved the retrobulbar tissue in 8 cases, the conjunctive in 7 cases and the lacrimal glands in 3 cases. The histological type, according to the WF was: low grade 13, intermediate grade 4 and high grade 1. Sixteen pts were treated with two anterior oblique wedged fields. The treatment was performed with a Linac (beam energy 5-6MV) in 13 pts, and with a 60Co unit in 3; in 7 pts a tissue equivalent bolus was added. The last 2 pts were treated with a single anterior electron field (beam energy 6 and 10 MeV respectively) using a lens sparing technique. Total dose ranged from 30 to 35Gy (less than 24 Gy in 11 pts) while the dose per fraction ranged from 1.5 to 2 Gy.

Results: All 18 pts obtained a complete still lasting local control. After a medium follow-up of 40.9 months (min 5, max 147, median 30.2), two pts developed systemic disease, respectively 8 and 50 pts after the first diagnosis. At progression these pts received chemotherapy and are still alive. Six pts developed cataracts that were operated in 3. No corneal ulceration or retinopathy were observed.

Conclusions: These data suggest that primary orbital lymphoma can be cured with moderate dose (30-34 Gy) radiotherapy with acceptable morbidity. Systemic disease occurring after radiotherapy procedures, is infrequent, thus it seems that there is no need for systemic therapy especially for low and intermediate grade lymphoma.


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NK cell lymphomas, encompassing the nasal and the "nasal type" varieties, are defined as angiocentric lymphoma in the R.E.A.L. classification. This entity is rare in the U.S.A. and Europe and more common in Asia and Caribbean Countries. It is associated with the EBV virus and its response to treatment and prognosis is usually very poor. The aim of our study is to describe our experience in 11 pts with this disease treated in MDACC in the last 7 years.

METHODS AND PATIENTS: Eleven pts with a diagnosis of nasal NK lymphoma were treated in MDACC since 1987. Typical immunophenotype expressing CD2+, CD3-, and CD56+ as well as non-rearrangement of T-receptors were present in all patients. Patients were treated initially with doxorubicin based regimens with radiotherapy in 10 cases and in one case after failing initial treatment with radiotherapy.

RESULTS: The median age was 46 y (15-67); there were 4 females and 7 males. Ten pts presented with local disease involving the sinonasal region and one patient with advanced disease in leukemic phase and with central nervous system involvement. Three pts presented B symptoms, 10 pts presented a performance status (PS) of 1 and one pt of 2. There were 6 out 11 responses (54%) with CR (36%) and 2 PR (18%). Three pts (27%) are alive with no evidence of disease (NED) at 1, 3 and 9 years after treatment; one pt is alive with disease (AWD) and a pt that died of other causes. Two pts received allogeneic BMT, one patient is alive in CR, NED 34 months after the bone marrow transplant. Six pts progressed of their disease in extranodal sites including testis (2), CNS (2), lung (1), bone marrow (2), liver (1) and peripheral blood (1).

CONCLUSION: NK nasal and "nasal type" lymphoma is a rare disease in U.S.A and Europe presenting commonly in the sinonasal tract with initially local symptoms. An elevated percentage of the patients are refractory to doxorubicin based regimen and radiotherapy. The disease tend to disseminate to extranodal sites including unusual involvement of testis, CNS and peripheral blood. Since the disease is associated with EBV virus in 90-100% of the cases and the prognosis is poor, innovative therapies including immunotherapy targeting the expression of the EBV by the tumor, with or without myeloablative procedures should be tried.

PRIMARY LARGE CELL GASTRIC LymphOMA: M.D. ANDERSON CANCER CENTER 40-YEAR EXPERIENCE

Objective: Primary gastric lymphoma is the most common presentation of extranodal Non-Hodgkin's lymphomas, yet is a rare disease. While the low-grade B cell lymphoma of MALT type have a favorable prognosis, the prognostic significance of other histologic subtypes remains to be defined. The purpose of our study is to evaluate the outcome, following different treatment approaches, of a large series of patients with primary large cell lymphoma of the stomach. Methods: A total of 120 patients (pts) with diffuse large cell primary gastric lymphomas were treated at our institution between 1959 and 1995. Data from 52 pts have been analyzed at this time. All pts, except two received chemotherapy with an anthracycline-based regimen. Twelve received chemotherapy plus radiation therapy; 18 pts underwent surgery combined with chemotherapy, radiotherapy or both. Fourteen received chemo alone. Results: Among the 52 pts, 35 were male (67%) and 17 (33%) female with a median age of 65. The most common presenting symptoms epigastric pain (80%) and GI bleeding (20%). Systemic B symptoms were present in 9 cases. Staging was according to the modified Ann Arbor staging system: stage I- 2.2%; stage II- 5%; stage III- 18%; stage IV- 5.3%. The median follow-up is 96 months. Four pts were refractory to treatment and died of disease. Forty-eight pts were disease-free at the completion of treatment. Seven patients (14.5%) developed recurrence and 5 of them died of progressive disease. Disease-free survival rates were 86% for the whole series, 95% for stage I and 88% for stage II disease. Five-year overall survival rates were 66% for the whole group, 86% for stage I and 67% for stage II disease. Conclusions: Patients with limited disease have a favorable outcome with chemotherapy alone or combined modality treatment. More advanced stages have a worse prognosis despite treatment with combined modality. Due to the rarity of disease, prospective multicentric studies are needed. Final data on the whole series of patients will be presented.

EXPRESSINOf POTENTIALLY ONCOGENIC HIV-8 GENES IN HIV-EBV NEGATIVE PRIMARY EFFUSION LYMPHOMA (PEL).
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Introduction: PEL is a novel lymphoproliferative disorder associated with the HIV-8 infection. The neoplastic transforming ability of HIV-8 has been observed by the fact that PEL arise in HIV-positive individuals, and are commonly positive for EBV, with these viruses having been related to the development of lymphomas. However, the existence of rare HIV-8, EBV-negative PEL cases suggests that HIV-8 may be pathogenic by itself, and offers a HIV-, EBV-negative setting to explore the possible lymphomagenic role of HIV-8.

Materials and methods: The expression of seven potentially oncogenic HIV-8 genes (Cyclin D, bcl-2, G-protein coupled receptor, IL-6, FLICE inhibitory protein, interferon regulatory factor, and ORF K1, a HIV-8 equivalent to the gene encoding herpesvirus saimiri transforming protein), was assessed by RT-PCR in an EBV-negative PEL presenting as a lymphomatous ascites in a HIV-negative patient. High molecular weight DNA was obtained from frozen cell pellets by a standard proteinase K/RNase treatment and phenol-chloroform extraction. Total RNA was isolated from cell pellets by the TRI reagent nuclear acid extraction kit. HIV-8 was demonstrated by PCR amplification of the KS13030 sequence and Southern blot analysis. The sequences of the primers and probes for the detection of transcripts from the seven genes were designed according to data submitted to the GenBank (accession no. U90543). The PCR products were detected by a chemiluminescence assay.

Results: DNA amplification bands of the seven aforementioned HIV-8 genes were identified with the expected size, with this confirming the presence of mRNA transcripts in this PEL. No cDNA amplification was observed in negative controls. The specificity of the amplification was demonstrated by hybridization of the PCR products to fluorescein-labeled internal oligonucleotides and observation of chemiluminescent signals with the expected size.

Conclusions: The expression of potentially oncogenic HIV-8 genes in this HIV-EBV-negative PEL case suggests that HIV-8 may be responsible for the transformation of B-lymphocytes through different molecular pathways in the absence of EBV infection.

6. Extramedullary Lymphomas
PRIMARY CUTANEOUS PLASMACYTOMA: A RARE ENTITY. DESCRIPTION OF A CASE AND REVIEW OF THE LITERATURE
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Background: Primary cutaneous plasmacytoma (PCP) is listed as a provisional entity in the EORTC classification of cutaneous lymphomas because of limited extensive case series and treatment data. We present a case and review the data reported in the literature.

Case report: A 53-year-old man presented with two erythematous nodules on the upper trunk. Histological examination (total body CT scan, bone marrow aspiration and biopsy) excluded an extracutaneous localization. The patient was treated with melphalan and prednisone obtaining a partial response, and subsequently with local radiotherapy, obtaining a complete response. The patient is alive and well 25 months after first diagnosis.

Discussion: PCP is a rare entity; only 31 cases were published in the last 50 years. The mean age is 60.5 years, the M:F ratio is 4:1. A solitary lesion was observed in 60% of the cases, the others showing multiple lesions. A monoclonal serum paraproteinemia (PP) at diagnosis was observed in 22 patients, whereas the presence of amyloid in the tumor was reported only in 3 cases. Treatment strategies ranged from surgical excision to radiotherapy and chemotherapy. 64% of patients presenting with a single lesion is alive and well after a mean follow-up of 5 years, 14% had local recurrence, and 21% had extracutaneous localization. Evolution to multiple myeloma was observed in 25% of patients with multiple cutaneous lesions. The presence of PP does not seem to influence the outcome. The prognosis of PCP is mainly related to the clinical presentation (single vs. multiple lesions). Local treatment (surgical excision, radiotherapy) can be effective in localized forms, whereas the role of systemic chemotherapy needs yet to be defined. The data confirm the existence of PCP as a distinct entity among primary cutaneous B-cell lymphomas, with a relatively good prognosis. Similarity to other forms of localized plasmacytoma (solitary plasmacytoma of bone), evolution into multiple myeloma is possible, especially in patients presenting with large tumors.

LONG TERM FOLLOW-UP OF GASTRIC MALT LYMPHOMA AFTER ERADICATION OF HELICOBACTER PYLORI INFECTION
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Several epidemiologic, experimental and clinical data suggest a link between mucosa-associated lymphoid-tissue (MALT) lymphoma of the stomach and gastric Helicobacter pylori (H. pylori) infection. Although many studies have reported a high regression rate for low-grade gastric MALT lymphomas (LGMLL) after anti-H. pylori therapy, we do not know whether H. pylori eradication and histological regression influence the natural history of LGMLL. At present, there are not long-term follow-up studies on LGMLL, so we have evaluated the outcome of 16 patients (pts) of a published previous multicentric series, referred to our centre from 1991 to 1994, with histological diagnosis of stage III LGMLL of the stomach, treated only with anti-H. pylori therapy. Follow-up included endoscopic investigation with biopsy samplings every 6 months and a re-staging every year. Response was evaluated using the histological score proposed by Wachter et al. (score < 3 = CR, score 3 = PR and score > 3 = NR). After eradication of H. pylori infection (achieved in all pts) dyspeptic symptoms disappeared or markedly diminished and endoscopic features improved in all pts. During the endoscopic follow-up, a multifocal disease was seen in 5 pts and change of gastric site in 3 pts; moreover we observed a continuous fluctuation of the histological score in most pts without any evidence of Hp reinfection. Thirteen pts achieved a complete remission (score 0-2) at least once during the follow-up, with a median time to obtain the regression of 19 months (range 2-54). Three pts, all affected by autoimmune disease, had no response after 45, 47 and 52 months, respectively. After a mean follow-up time of 61 months (range 44-87), in only 3/13 pts a complete remission (score 0-2) still persists in the whole stomach; 2/13 pts relapsed respectively after 3 and 30 months; 3/13 actually present a score 0-2 and 5/13 pts a score 3, all after continuous histological score fluctuations.

Conclusion: Considering the long follow-up time, our data, in agreement with other reports, support the favourable clinical behaviour of LGMLL, but underline that LGMLL is a multifocal disease with many different loci showing different histological features, so it could be difficult to demonstrate a regression even with a large number of biopsies. At present, we do not know whether the regression of histological score of MALT lymphomas after H. pylori eradication reflects a real remission of the disease or the different aspects of a multicentric disease detected in multiple random biopsies. Anyway, in our long follow-up study, after H. pylori eradication, a progression from low-grade to high-grade MALT lymphomas was never detected.

LOW DOSE 2-CHLOROXYDENOSINE FOR THE TREATMENT OF MYOCOSES FUNGOIDES
F. Traininger, J. Schwarzmeier, H. Hsingkum, and R.M.Krohler
Division of Special and Environmental Dermatology, Dept Dermatol; Dept of Internal Medicine, Univ.of Vienna, Austria

Introduction: 2-Chloroxydenosine (2-CDA, Cldirubine) is a nucleoside analogue with cytotoxicity to both resting and dividing lymphocytes and with clinical activity against hairy cell leukemia and low grade lymphomas including cutaneous T-cell lymphomas. This early phase II study was initiated to evaluate the clinical efficacy and the side effect profile of a low dose regimen of 2-CDA in the treatment of mycosis fungoides (MF).

Methods: Eight patients with MF were included in this study (2 pts: stage IB, 3 pts: stage IV A, 3 pts: stage IV B). 2-CDA was administered by i.v. infusion at a dose of 0.1 mg/kg/day for five consecutive days. Cycles were repeated every four weeks for up to a maximum of 8 cycles.

Results: 2 of 8 patients had a partial remission, which lasted 13+ and 12 months, and one patient stable disease (6 months) (table). Side effects were mild (reversible lymphopenia, WHO grade 0-1). One patient in advanced stage IV A developed severe infection without myelosuppression after 2 cycles. Other toxicity (alopecia, nausea, vomiting, stomatitis, diarrhea, organ toxicity) was not observed.

<table>
<thead>
<tr>
<th>Pt</th>
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<th>Age</th>
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<th>Cycle</th>
<th>Response</th>
<th>Side Effects</th>
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<tr>
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</tr>
<tr>
<td>2</td>
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<td>52</td>
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<td>8</td>
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<td>lymphopenia</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>69</td>
<td>IV A</td>
<td>1</td>
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<td>IV B</td>
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<td>8</td>
<td>F</td>
<td>72</td>
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</table>

Conclusion: This study shows that, when compared to a standard dose regimen, low dose 2-CDA has a predictable toxicity profile, making this treatment suitable for low grade T-cell lymphomas of the skin. Phase II phase and phase III studies appear justified to determine the comparative efficacy of low dose 2-CDA to other treatments.

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<td>1</td>
<td>PD</td>
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MONOCLONAL B-CELLS IN GASTRIC MALT LYMPHOMA IN COMPLETE REMISSION: MOLECULAR STUDIES ON MICROSIZED CELLS

C. Thiele*, T. Wüstenhauopp, A. Alpepp*, B. Heubronn*, B. Beyenrieff* A. Heubronn*, M. Stute
*Medizinische Klinik I, Universitätsklinikum Dresden, Innen Klinik, *Thierry-Universität Münster, Institut für Pathologie, Klinikum Bayreuth, Germany

Background: Endoscopy of Helicobacter pylori has established as first line therapy in stage E1 low grade gastric MALT-B-cell lymphomas, including complete remissions (CR) in about 70-80%. PCR for the rearranged immunoglobulin heavy chain region (IgH) may be helpful in the differential diagnosis of gastric MALT lymphoma. However, its role in the follow up of patients after H. pylori eradication has not yet been fully understood. Sequence data indicate that the clones detected during the follow up were related to the original malignant B-cell clones. The topographic origin of the monoclonal B-cells is so far unknown.

Patients and methods: A semi-nested PCR for the rearranged IgH-variable region was performed on genomic DNA extracted from gastric biopsies from 90 patients with gastric MALT lymphoma and after eradication of H. pylori. Consensus primers for VH framework regions 1, 2 and 3 in combination with JH primers were used. Sections of paraffin-embedded biopsies of patients in complete remission and ongoing monoclonality were cut on slides (so far in 5 patients). Lymphoid cells of defined topographic origin were dissected under buffer solution, using an automated micromanipulator, then genomic DNA was extracted. Monoclonal PCR-amplificates were subcloned and analyzed by automatic DNA-sequencing.

Results: PCR was monoclonal in 64 patients (71%) at diagnosis. Follow up material was available in 46 patients in CR, five in PR and one showing NC. The PCR remained monoclonal in 24/46 patients in CR (52%) and all analyzed patients with partial or no response. The median PCR follow up time of patients in CR with monoclonal PCR was 583 days (range 6-1345 days). Of five patients in CR, who experienced local relapse of the lymphoma, the PCR remained monoclonal in four. DNA from lymphoid cells dissected from basal lymphoid aggregates showed identical VH-D-JH rearrangements as the original malignant B-cell clone, whereas lymphoid cells from other regions as the upper mucosal layers were not found to reveal any clonal relationship.

Conclusions: The PCR is continuously monoclonal in about half of all patients in complete histological remission, in some patients for up to 44 months. All patients without complete response and the majority of those patients showing a local relapse remained monoclonal in PCR. Microdissection results suggest basal lymphoid aggregates located in the gastric submucosa as source of monoclonal B-cells.

Non Hodgkin Lymphomas and Canec Disease

A. De Renzo, C. Catassi, E. Fabiani, B. Rotoli and the Italian working group on Canec Disease and Non Hodgkin Lymphoma Hematology Unit, Federico II University, Naples, Departments of Pediatrics and Internal Medicine, University of Ancona, Italy

Introduction: Canec Disease (CD) can be defined as a permanent intolerance to gluten, and is characterized by (sub)clinical villous atrophy in the proximal small intestine. In comparison to the general population, patients with CD have a higher relative risk of developing intestinal NHL, in particular a syndrome called enteropathy associated T-cell lymphoma (EATL). In previous studies, the prevalence of lymphoma complicating CD was extremely variable, ranging from 0 to 16%. Aim of our study is to quantify the risk of NHL in patients with CD and to characterize the spectrum of CD-associated NHL.

Methods: In a multicentric case-control study, NHL patients and healthy controls were tested for serum IgA anti-endomysium antibodies (IgA-AEA), and intestinal biopsy was performed in AEA-positive cases.

Results: From Jan 96 to Sept 98, 446 NHL patients were tested. Median age was 55.9 yrs (range 20-83), phenotype B 77%, T 9%, non specified 14%, primarily in the gut 12%. Four patients had fully documented CD (1 EATL, 1 ileal B-cell, 1 small intestinal T-cell and 1 mediastinal T-cell); in two additional patients (stomach B cell and tonal T cell, respectively) CD diagnosis was suspected but not proven because biopsy could not be performed (possible CD); in two other patients with T-cell NHL. AEA were positive but jejunal histology was normal (potential CD). In the control group (n=5098) there were 15 CD cases. The odd ratio of NHL was 4.1 (95% confidence interval: 1.4-11.8) considering only proven CD cases, and 2.9 (3.7-18.0) including probable and potential CD cases.

Conclusions: Compared to the general population, patients with CD have increased risk of NHL. CD-associated NHLs include not only EATL but also T cell and B cell lymphomas with intestinal or extra-intestinal involvement.
CONSERVATIVE THERAPY OF PRIMARY MALT GASTRIC LYMPHOMA
L. Orucu, B. Botto, M. Bertini, C. Becocim, R. Calvi, F. Ficara, P. Fregno, R. Freilone, U. Vitolo and E. Gallo. Department of Hematology, S. Giovanni Torino Italy

Introduction - Primary Gastric B Cell Lymphoma of the mucosa associated lymphoid tissue (MALT) is the most frequent extranodal form of NHL. In the past many patients underwent surgical resection. Currently the endoscopic diagnosis is possible in an increasing number of patients, these reduce the surgical approach to treatment. Moreover more than 90% of gastric MALT lymphomas are diagnosed in patients with chronic HP-associated gastritis. In limited stages of low grade gastric MALT lymphoma the cure of HP infection is associated with high remission rates. In 1995 we started a study of conservative therapy for primary gastric lymphoma; we treated 20 patients, median follow up is 24 months.

Patients and methods
The therapeutic approach is as follow:
A) low-grade gastric MALT lymphoma stages I-IIa: antibiotic therapy consisting of amoxicillin + clarithromycin + omeprazole for two weeks
B) low-grade gastric MALT lymphoma stages IIb + III: antibiotic therapy and chemotherapy chlorambucil 10mg/die for two weeks every month, for six courses.
C) high-grade localized gastric MALT lymphoma: ACM-P chemotherapy (Doxorubicin, Cyclophosphamide, Vincristine and Bleomycin) for six weeks + Radiation therapy IF 36 Gy
Results: Group A= 13 patients were treated; CR was achieved in 10; 1 patient was NK and referred to surgery and 1 patient obtained PR.
Group B= 4 patients were treated; CR was achieved in 3, and 1 patient was NK.
Group C= 4 patients were treated; all achieved CR.
Conclusion: conservative therapy in MALT lymphomas is feasible and surgery is not strictly required in the treatment of gastric lymphoma. The cure of HP infection is associated with high remission rates in limited stages of low grade gastric MALT lymphomas. These results must be confirmed by a higher number of patients.

CENTROFACIAL NON HODGKIN Lymphoma: A DEMOGRAPHIC ANALYSIS IN MEXICAN PATIENTS
Hematology and Clinical research departments, Instituto Nacional de Cancerologìa, México

Due to a high incidence of centrofacial NHL in our series, we analyzed our experience in this tumor, assessed demographic characteristics of 116 consecutive patients with or without nodal disease. Results are presented at the table.

<table>
<thead>
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<th>All (number)</th>
<th>Male (%)</th>
<th>Female (%)</th>
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</thead>
<tbody>
<tr>
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<td>Age</td>
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</tr>
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<td>II</td>
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<td>47</td>
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<td>III</td>
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<td>39</td>
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<tr>
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<tr>
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<td>11</td>
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<tr>
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<tr>
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<tr>
<td>Tumor size</td>
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<td>64</td>
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<tr>
<td>max. 10 cm.</td>
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<td>31</td>
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<tr>
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<td>59</td>
</tr>
<tr>
<td>Alive in PR</td>
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<td>2</td>
</tr>
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<td>39</td>
</tr>
<tr>
<td>Death by other disease</td>
<td>2</td>
<td>3</td>
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</tbody>
</table>

We did not found any IV clinical stage, also, there was a low percent patients in high risk prognostic index and a very large proportion of patients with big mass tumor. Nevertheless, clinical response was acceptable. All of this suggest a local disease with a different biology and outcome.

PROGNOSTIC FACTORS IN PRIMARY CUTANEOUS B CELL LYMPHOMA, AN ANALYSIS OF 54 CONSECUTIVE PATIENTS
U. Naldi, L. Magrini, S. Cortelazzzo, A. Rossa, E. Oldani, T. Motta, T. Canelli, T. Barbi
Department of Dermatology, Hematology, and Pathology, Ospedali Riuniti, Bergamo, Italy

Introduction - Little is known about the long term outcome of lymphoma primarily affecting the skin. The purpose of our study was to analyse prognostic factors in a group of patients with primary cutaneous B cell lymphoma.

Patients and methods - A total of 54 consecutive patients receiving a first diagnosis of cutaneous B cell lymphoma at our institution, in the period January 1988 to December 1997, were assessed. The diagnosis was based on morphologic characteristics and immunophenotyping. Staging procedures included chest and abdominal tomography and bone marrow biopsy. There were 32 men and 22 women. Median age at diagnosis was 54 years (range 23-80). A total of 41 cases were classified as low grade malignancies and the remaining 13 cases as high grade. Low grade solitary lesions were treated with radiotherapy or surgical excision; chlorambucil monotherapy was added for the treatment of low-grade multiple lesions. High grade malignancies were usually treated with six to eight cycles of standard polychemotherapy.

Results - After a median follow-up of eight years (range 1 to 11 years) a total of 41 patients (77%) were in 1st continuous complete remission. The 5-year overall survival and event free survival were 92% and 81% respectively. In multivariate analysis (Cox regression model), location on the legs was the only significant prognostic factor for a unfavourable outcome (RR 3.0; 95% CI 1.2 to 7.2).

Conclusions - Our data suggest that location on the legs carries per se a worse prognosis in cutaneous B cell lymphoma.

PURE EXTRANODAL LYMPHOMA (PEL) IN MEXICAN PATIENTS: DEMOGRAPHIC ANALYSIS
Muñoz D, Mariscal RI, Dueñas A, Cervera E, Sobreviella-Calvo P, Mohar A, Labardini J
Hematology and Clinical research departments, Instituto Nacional de Cancerologìa, México

PEL is not an uncommon disease. We reviewed on a retrospective fashion, clinical records from PEL patients in order to know main clinical and demographic data. We found 80 patients with extranodal lymphoma and no clinical or radiological evidence of nodal disease. There were 42 males (52.5%) and 38 females (47.5%) with mean age of 50 yo (range 18-90). Centrofacial (CL) was the most frequent involved site (31 pts), followed by stomach, bowel, central nervous system, soft tissue and bone marrow (18,10,6,5 and 4 pts respectively). 32 pts had two or more extranodal involved sites. 30% of pts. had mass tumor less than 5 cm, and 35% with more than 5 cm. Very large mass tumor, more than 15 cm was seen in 5%. LDH was elevated in 31%, most pts. had limited disease (61%, Ann Arbor stage I-II) and were ambulatory at diagnosis (85%, PS 0-1). International index distribution was 49, 37, 8, 6 % for low, low intermediate, high intermediate and high groups respectively. Diffuse large cell, mixed diffuse, immunoblastic and non classifiable were the predominant histology (45%,19%,15%,15% respectively). Most pts were treated with anthracycline-based chemotherapy regimens, and no difference was seen among them. We found complete response in 60%, progressive disease in 15%, partial response in 4%, early death in 6% and 19% were lost to follow-up. We found no statistical difference in complete responses among different types of PEL. CONCLUSION: We found a very high incidence of CL among PEL. This could be due to referral bias in a third level cancer center or could represent a true ethnic, environmental or biological expression of lymphoma in latin-american pts.
GASTRIC NON HODGKIN LYMPHOMA (GNHL) IN MEXICAN PATIENTS: A DEMOGRAPHIC ANALYSIS
Haematology and Clinical research departments, Instituto Nacional de Cancerologia, México

GNHL is the most frequent extranodal lymphomatous tumor, we analyzed retrospectively our experience, assessed demographic characteristics of 55 consecutive patients treated at our institute. Our results are presented at the table.

<table>
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<tr>
<td>Early</td>
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<td>23%</td>
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<tr>
<td>II</td>
<td>5</td>
<td>6%</td>
<td>13%</td>
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<td>III</td>
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<tr>
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<tr>
<td>more than 10 cm</td>
<td>14</td>
<td>28%</td>
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<td>50%</td>
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<tr>
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<td>28%</td>
<td>31%</td>
</tr>
<tr>
<td>Death by disease</td>
<td>19</td>
<td>38%</td>
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<tr>
<td>Lost</td>
<td>18</td>
<td>31%</td>
<td>34%</td>
</tr>
</tbody>
</table>

We found a low surviving rate, due to advanced stages at presentation and correlate with high prognostic indexes, all may be by aggressive different biology or delay in diagnosis and treatment.

RADIOThERAPY AND CHEMOTHERAPY (RT/QT) VERSUS RADIOThERAPY ALONE (RT) IN THE MANAGEMENT OF PRIMARY CENTRAL NERVOUS SYSTEM (PCNS) LYMPHOMA IN HIV NEGATIVE PATIENTS
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We retrospecively analyzed data on 11 consecutive HIV negative patients with PCNS NHL, treated at our institute over the last 5 years with (RT/QT) or (RT). We assessed the clinical outcome of these patients among two groups. There were 7 males, 4 females, with a mean age at diagnosis of 46 (17-85). All patients had biopsy proven disease and all of them were diffuse large cells. No one of them had any other site of disease. They had an average number lesions of 2 (1-6), 54% presented with solitary masses. Four patients received RT/QT, CHOP at regular doses for a mean of 6 cycles, and irradiation to the brain by means of two opposite lateral fields, the medium dose of radiation was 50 Gy (50-80); two of them have complete response by surgical procedure. Five patients received radiotherapy alone, by same fields and doses. Two patients declined to receive any kind of treatment (one was dead, another was lost). Four patients achieved CR, all of them received RT/QT. One experienced recurrence at 3 months following CR. At the time of analysis, 3 patients are still alive in CR. Patients with complete surgical resection are still alive and in first remission. One who received RT alone achieved CR. Median follow-up at surviving patients was 20 months. 6 have died and two were lost. Toxicities were similar in both groups. In our experience RT/QT is better than RT alone, without additional toxicities. Complete surgical resection may be a determinant prognostic factor.

PRIMITIVE EXTRANODAL LYMPHOMA OF THE MEDIAN NERVE.
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Among the primary extranodal lymphomas the localization to the peripheral nerves is very uncommon. Rare cases are reported in literature; often they are T-cell, but also B-cell lymphomas are described. The involved nerves are the sciatic, the acoustic, other cranial nerves. We have observed a patient with a solitary lymphomatous lesion of the median nerve of the left arm. The patient, O.S.G., a white male HIV seronegative, aged 55, presented a mass of the middle third of the left arm, along the course of the median nerve. No systemic symptom was present. The mass was completely removed and the histologic examination showed a massive infiltration of the nerve structure by large neoplastic cells LCA and CD20 positive. The diagnosis was: Large B-cell lymphoma involving the median nerve. He underwent a complete routine staging procedure, with blood chemistry, total body CT scan and bone marrow biopsy; no other localization of the disease was found. The x-LDH was within normal range and the Performance status was quite good (WHO = 0). Serum and urine immuno-electrophoresis were normal. No sign of active infection were found for CMV, herpes virus, HCV, HVB. The patient was treated with MACOP-B, local radiotherapy was not administered because of the tumor was completely surgically removed. Now the patient is in continuous complete remission after 9 months after the end of the treatment.

In the last years, to the best of our knowledge, the isolated infiltration of the median nerve has been reported only in two other cases of lymphoma. However in one case it was consistent to the localization of the disease to the supratrochlear lymphnodes, while in the other it was the site of recurrence of the disease. The peripheral nervous system may be involved by a lot of neurological and sytemic diseases. Also lymphoproliferative disorders with various mechanisms may damage the peripheral nerves: paraneoplastic, treatment toxicity, compressive, infectious, infiltration by monoclonal immunoglobulin. Among these clinical conditions also the primitive lymphomatous infiltration must be taken into account.

CREMO-RadiOTHERAPY IN PRIMITIVE CEREBRAL LYMPHOMA
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From 1995 to 1998 we observed in our University 16 HIV negative PCL patients at the diagnosis (8 males and 8 females, aged 38-71, median 54). In all cases the diagnosis was made by histological examination of the neoplastic cerebral tissue. All cases, but one, were large B cell (REAL classification); the last was a T cell angiocentric lymphoma. They were planned to receive chemo-radiotherapy with the following schedule.

Systemic chemotherapy: Methyltreon (MTX) 3 g/m² with folinic acid rescue. day 1, 22 ; Ara-C 3 g/m² : day 4, 44, 64, 65. Intrathecal chemotherapy (by intraventricular catheter). MTX 12 mg: day 0, 12, 20; Ara-C 50 mg: day 3, 16, 24.

Radiotherapy. (RT) Whole brain +/- boost: 45-60 Gy within 1 month after chemotherapy.

Three patients died during the treatment and received only a partial chemotherapy, while in other 3 cases the progression of the disease or the lack of response to the MTX induced us to use a sandwich schedule MTX – RT – AraC. In 1 of these a surgical debulking was performed before the RT. One patient is still on therapy and is not evaluable. Twelve patients completed the treatment and 8 achieved the CR, 3 had a PR and 1 had a progressive disease. Among the 8 CR patients 5 are in CR, 1 died for respiratory causes, 1 relapsed and died after 15 months, one, relapsed after 1 month, received a 2nd line treatment and ABMT and now is in 2nd CR lasting 9 months. Among the PR patients 2 died and 1 is receiving 2nd line therapy as well as the patient with the progressive disease.

The analysis of survival of the 13 patients who completed the treatment (Product limit method of Kaplan Mayer) showed a median survival of 31 months. Examining the patients according to performance status (PS) (WHO) in univariate analysis we observed that the subjects with PS ≤2 presented a better survival (PS≤2 median not reached, PS>2 median survival 11 mo); also younger patients (age ≤50) seem to have a better prognosis (all alive vs a median survival of 11 mo for the older patients). Venous thromboembolism (VTE) (4 cases, with 1 death for pulmonary embolism) was a frequent complication of our series.

In conclusion we retain that the combination of radio-chemotherapy can represent a good approach to the PCL, overall for young patients in good performance status. The frequency of VTE induce us to recommend the use of antithrombotic prophylaxis.

6. Extranodal Lymphomas
Gastrointestinal Non-Hodgkin's Lymphoma - a retrospective analysis of 34 cases.
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Introduction: Non-Hodgkin's lymphoma of gastrointestinal tract (GIT) has been reported as the most frequent extramodal site of NHL. It accounts for 30% or more of all primary extramodal lymphomas. The treatment of patients with primary gastrointestinal tract lymphoma is still very controversial. We analysed the results of different modalities of treatment.

Materials and methods: A retrospective analysis of 34 patients (pts) with non-Hodgkin lymphoma of gastrointestinal tract treated in our Institute between 1985 and 1998 has been conducted. The mean age was 49 years (range 30-73) with a female to male ratio of 1:2.7. The most frequent primary site of disease was stomach - 24 pts (71%), small intestine - 7 pts (20%), large intestine - 2 pts (6%), rectum - 1 pt (3%).

Patients were clinically staged according to the Ann Arbor classification - 22 patients (64.7%) were early stage (I-E I-E II), 12 patients (35.3%) had advanced disease (III E and IV E). All histologic material was reviewed and classified according to Kiel classification - 20 pts (58%) low grade, 14 pts (41.2%) high grade GI lymphomas. Four patients (11.7%) were treated with chemotherapy alone (CT); 19 pts (56.1%) had surgery and chemotherapy (S+CT); 4 pts (11.7%) had surgery and radiotherapy (S+RT); 7 pts (20.5%) surgery and chemotherapy alone, and radiotherapy (S+CT+RT). Patients treated with chemotherapy received multidrug treatment (COP, CHOEP). Patients treated with radiotherapy received total tumor dose in the range of 40.0 to 46.0 Gy (mean 43.7 Gy). The observation time is from 1 - 137 month (median 24 months).

Results: CR was achieved in 70% of pts in all the group. Among them 21/22 (95%) pts with early stage (IE, IIE) and 5/12 (25%) pts with advanced disease (III E, IV E) CR was observed in 13/20 (65%) of pts with low grade lymphoma in comparison to 10/14 (71%) of pts with high grade lymphoma. CR was achieved in 14/19 (74%) 4/7 (57%), 4/4 (100%) and 2/4 (50%) patients treated with (S+CT), (S+CT+RT), (S+RT) and chemotherapy alone respectively. 5 year overall survival (OS) rate was 80% for all the group. Among pts with early stage lymphoma 74% comparing to 91% in pts with advanced disease. There was no significant difference in 5 year OS between pts with low grade and high grade lymphoma (80% vs 91%).

Conclusions: Better results in terms of CR rate were observed in pts with early stage lymphoma comparing to the pts with advanced stage (95% vs 25%). 65% pts with low grade lymphoma achieve CR versus to 75% pts with high grade. There was no significant difference in terms CR rate and survival between the pts in regards to different modalities of treatment, or pathological classification (low vs high) of lymphoma.

FOLLICULAR MYCOSIS FUNGOIDES
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The spectrum of mycosis fungoides is exceedingly broad and includes different variants. A rare form which shows destruction and infiltration of hair follicles by malignant lymphocytes is follicular mycosis fungoides. We reviewed our experience with eight cases of follicular mycosis fungoides. The common feature was infiltration and destruction of the hair follicle epithelium by atypical lymphocytes. In some specimens the lymphocytes displayed only minor atypia leading to misinterpretation as pseudolymphoma. Gene rearrangement studies were helpful for establishing a diagnosis of malignant lymphoma. Interestingly, mucin deposition was present to varying degrees making the distinction from mycosis fungoides-associated follicular mucinosis difficult. In one patient, we found both dermal mucin and a follicular mucinosis pattern present at different stages of disease. In conclusion, we suggest the term mycosis fungoides-associated follicular mucinosis should be replaced by follicular MF in future lymphoma classification schemes.
EXPRESSION OF CD10, CD75 AND CD43 IN MALT LYMPHOMA AND ITS USEFULNESS IN DISCRIMINATING MALT LYMPHOMA FROM FOLLICULAR LYMPHOMA AND CHRONIC GASTRITIS

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Introduction: While it may be difficult to discriminate between chronic gastritis, MALT lymphoma and a gastric localisation of a nodal lymphoma using histology of small endoscopic biopsies alone, additional markers like CD10, CD75 and CD43 and proliferative activity may be of value. The expression of these antigens in MALT lymphoma and their usefulness in discriminating MALT lymphoma from follicular lymphoma on the one hand and gastritis on the other hand is evaluated.

Methods: Tissue samples of 38 patients with gastric MALT lymphoma were immunohistochemically stained for expression of CD10, CD75 and/ or CD43. Proliferation index was scored using MIB-1 staining. Results: Ten cases of nodal follicle centre B-cell lymphomas (n=11) and 18 cases of high grade MALT lymphomas (n=22) show moderate to high CD75 expression (25-100% positive cells). All tested low grade MALT lymphomas (n=9) and chronic gastritis (n=6) are negative (0-25%) for CD75. All MALT lymphomas (n=25) are negative for CD10. High grade lymphomas show significantly higher proliferation indices (67% vs. 16%) than low grade lymphomas. Only 4 of 26 MALT lymphomas were slightly positive for CD43. All gastritis biopsies (n=4) are negative for CD43.

Conclusions: These data suggest that combining both CD10 and CD75 may be useful in discriminating between low grade MALT, high grade MALT lymphoma and extranodal localisation of follicular lymphoma. However, CD43 expression can in the majority of cases not be used to distinguish between low grade MALT lymphoma and gastritis.

FREQUENT OCCURRENCE OF CLONAL T CELLS IN THE PERIPHERAL BLOOD BUT NOT IN THE SKIN OF PATIENTS WITH SMALL PLAQUE PARAPROTEINEMIAS

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Introduction: Clinical, immunohistological and molecular biological data suggest the chronic dermatosis small plaque paraproteinemia (SPP) to be a precursor of cutaneous T cell lymphoma (CTCL), in particular of mycosis fungoides (MF). Recently, clonal T cells were detected in skin and blood samples of early MF. Since demonstration of clonal T cells in both compartments would indicate the systemic character of SPP and its close relationship to MF as well as facilitate prediction of the clinical course and selection of therapy modalities, we asked whether T cell clonality is also detectable in skin and blood specimens of SPP patients.

Methods: According to strict clinical and histological criteria, fourteen SPP patients were selected and blood and skin specimens were taken at the initial diagnosis. During the follow-up of 18 to 47 months, one to 8 additional blood samples were collected per patient. T cell clonality was investigated by a PCR amplifying T cell receptor γ rearrangements and subsequent heteroduplex loaded temperature gradient gel electrophoresis (PCR/HD-TGGE). According to the sequence of the predominant TCγ rearrangement, clone specific PCR assays were established.

Results: Clonal T cells were demonstrated by PCR/HD-TGGE in 7/14 initial blood samples, but in 0/14 initial skin specimens. Data obtained from peripheral blood were confirmed in 4/7/48 follow-up samples. Clone specific PCR assays were established in 6/9 SPP cases carrying circulating clonal T cells. These assays demonstrated the persistence of the initial T cell clone in 2/20 study patients for up to 20 years. Stem cells from a SPP individuals was not correlated with changes in clinical markers previously found to be risk factors for disease progression in CTCL.

Conclusions: For the first time, the majority of SPP patients was demonstrated to carry a persistent T cell clone in the peripheral blood. Although a relation between circulating clonal T cells and SPP cannot directly be proven by the applied techniques, our results indicate blood T cell clonality to be a specific feature of SPP and CTCL since analysis of multiples controls and clinical workup of our SPP patients excluded other factors simulating or causing a clonal T cell proliferation. A sufficient unifying anti-tumor response but also an extracutaneous origin of the T cell clones might explain the failure to detect skin infiltrating clonal T cells.

RETROSPECTIVE SURVIVAL ANALYSIS IN GASTRIC LYMPHOMA REVEALS SURGICAL THERAPY AND MALT HISTOLOGY AS FAVOURABLE PROGNOSTIC FACTORS

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Background: Primary gastric lymphomas is a condition with a pathogenesis and biology different from primary nodal lymphomas. Its prognosis seems to be more favourable than nodal NHL. However, there is still no general agreement on the treatment of choice in primary gastric NHL.

Study design: The present population-based study retrospectively summarizes the presentation, histopathology, treatment and survival of 69 consecutive patients with primary gastric NHL. In addition to the clinical description of these cases, we tried to analyse the role of surgery in the treatment of gastric lymphomas, and to identify prognostic factors.

Materials and methods:Thirty-seven male and 32 female patients with a median age of 67 years were studied. They were classified as small cell MALT NHL (n=27), large cell MALT NHL (n=22) and large B-cell NHL (n=20).

Results: Abdominal pain, dyspepsia and weight loss were common complaints at presentation. The majority of patients presented in clinical stage I, without a significant difference in the three distinct groups. Forty-four patients underwent surgical therapy (17 of which in combination with chemotherapy and 5 with radiotherapy). Twenty-one patients received chemotherapy only. Overall five-year survival was 65%, whereas the projected ten-year survival was almost 37%. Small cell lymphomas, MALT lymphoma, surgery, low stage (I, II) and younger age were associated with longer survival, whereas the presence of p53 protein overexpression signified a poor prognosis. In a multivariate analysis, the presence of MALT and younger age were the only significant prognostic factors. To examine the role of therapy, only factors known at presentation were entered in the Cox regression. This procedure revealed surgery as the most important prognostic factor.

Conclusions:Gastric lymphoma with MALT component is associated with a better overall survival. Furthermore, within the limitations of this retrospective analysis, surgically treated patients had a more favourable prognosis.

CRITERIONS FOR MORPHOLOGICAL DIAGNOSIS OF DIFFERENT GRADES OF MALTOMA'S MALIGNANCY

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Introduction: MALT lymphoma is a heterogeneous tumor population with different cell composition and variants of growth, which stipulate for features of clinical behavior. The purpose of our study was to distinguish several grade of MALToma's malignancy for formation of corresponding clinical groups using parallel histological and cytological methods.

Methods: We used gastroscopy and surgical material for both histological and cytological investigations from 44 patients (31-78 years old). Value of Helicobacter pylori was semiquantitative in histo- and cyto-preparations. All diagnosis of MALT lymphomas were confirmed using immunomorphology.

Results: MALT-lymphomas were divided into 3 groups according to grade of malignancy:

1) Low grade MALTomas were presented with well-differentiated, dense mass, formed by centrocyte-like and like small lymphocytes cells. CEL and H pylori (negative grade) were noted in all cases. The increase of blast cells, follicle colonization by mature tumor cells, the infiltration of small follicles of blasts, a diffuse composition of blasts and differentiated cells.

2) Low grade/high grade MALTomas: the predominance of differentiated cells in the tumor mass was necessary condition and the signs of blast transformation were considered: a) within the 'matutic tumor cells' infiltrate the presence of small foci of blasts; b) a diffuse composition of blasts and differentiated cells.

3) High grade MALTomas were presented with a majority of blast cells-like centroblasts and immunoblasts - sheets. CEL was forming by blast cells. Conclusion: An adequate clinical approach may be postulated on the basis of the above described grade of malignancy.

6. Extranodal Lymphomas
Total Skin Electron Irradiation in Mycosis Fungoides:

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ABSTRACT

Fourteen male patients between 27-82 years with mycosis fungoides were treated with total skin electron irradiation (TSEI) between 1985 to 1998. All the patients were male and seven patients were having early stage disease, whereas rest of the patients had advanced diseases. Two patients had lymph node involvement at presentation. The total skin electron irradiation with electron beam was performed according to Stanford technique. The total dose of radiotherapy delivered was in the range of 36-36 Gy. The eyes and nails were shielded at each session of radiotherapy. Out of those 14 patients, who could complete the treatment, eleven patients had complete remission following TSEI. The total follow up period was up to 110 months, the median being 52 months. Relapse of the cutaneous lesions occurred in three patients after 2-27 months. One patient developed visceral involvement. Five patients were alive without the disease at the end of 5 years.

Key Words: Mycosis Fungoides, Total skin electron irradiation, Treatment