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Cardiac lesions after mediastinal irradiation (r) for Hodgkin's disease (HD)

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Purpose: Analysis of the risk of cardiac r with a low dose per fraction and an intermediate total dose with or without chemotherapy (c).

Methods: Between 1964 and 1992, 367 patients with HD had curative r with or without c including the mediastine. The mean length of follow up is 11 2 years with a range between 1 and 32 years. 97% of the patients have a complete follow up and 155 (64% of the living patients) consented in a special heart examination including: rest and exercise ECG, echocardiography and myocardial perfusion scintigraphy. Risk factors were also evaluated: body mass index, blood pressure, smoking history, diabetes mellitus, cholesterolemia and cardiac disease before r. In 97% of the patients, the dose per fraction in the anterior heart was between 1.3 and 2.1 Gray with a total dose between 30 and 42 Gray.

Results: The risk of fatal cardiac ischemic events (mi) and/or a sudden unexpected death (sd) was significantly higher than expected with a relative risk of 4.2 for mi and 6.7 for mi or sd. The actuarial incidence of fatal or non fatal ischemic cardiac events or of sd or of congestive heart failure was 3.6% after 10 years, 12.9% after 20 years and 41.7% after 30 years. In the patients without risk factors this incidence was 1.3% after 10, 20 and 30 years, not significantly different from the expected value. In patients without risk factors and without c there was no ischemic or other cardiac event. Actuarial incidence of valvular thickenings after 30 years was 60%, mostly without hemodynamic disturbance. C including adriamycin was not a risk factor for cardiac events.

Conclusion: After r of the heart with a low dose per fraction and an intermediate total dose, the incidence of major ischemic cardiac events is significantly higher than expected. But in patients without other cardiovascular risk factors, this risk seems low. C including adriamycin with a total dose between 150 and 300 mg/m2 did not increase this risk. Valvular thickenings are frequent but mostly without hemodynamic disturbance.

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Clinical factors predictive of the probability of upstaging patients with clinical stage (CS) I or II supradiaphragmatic Hodgkin's disease (HD) to pathological stage (PS) III_2 or IV by staging laparotomy

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Background: Some studies have shown that certain clinical factors predict the probability of abdominal involvement in patients with CS I and II disease. The identification of the clinical factors that predict the probability of upstaging patients with CS I or II to PS III_2 or IV would be useful for treatment selection since these patients would be at high risk of relapse following radiotherapy alone.

Patients and Methods: We reviewed the results of surgical staging in the 361 consecutive patients with CS I or II Hodgkin's disease admitted at our department between 1970 and 1985, all of whom underwent staging laparotomy. We performed a multivariate analysis to identify the clinical factors predictive of the probability of upstaging those patients to PS III_2 or IV.

Results: Out of 361 patients, 39 were upstaged to PS III_2 or IV The three factors found to significantly influence the probability of upstaging to PS III_2 or IV were fever [present *vs* absent: relative risk (RR): 9.68; 95% confidence interval of the relative risk (95% CI): 4.44–21.11; $P < 0.0001$], number of involved nodal sites [≤ 4 *vs* >4 sites: RR: 8.17; 95% CI: 2.51–26.56; $P < 0.001$] and mediastinal involvement [normal mediastinum *vs* nonbulky mediastinal disease: RR: 0.24; 95% CI: 0.08–0.70; $P < 0.01$ and normal mediastinum *vs* bulky mediastinal disease: RR: 0.25; 95% CI: 0.09–0.68; $P < 0.01$]. According to these results, the predicted probability of upstaging a patient with a number of involved sites ≤ 4 and no fever to PS III_2 or IV was lower than 10%.

Conclusions: The results of this analysis suggest that certain clinical factors are useful to identify those patients with high and low risk of having extensive abdominal nodal or extranodal disease disclosed by surgical staging.

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Intermediate-high dose sequential single agent chemotherapy combined with irradiation in advanced Hodgkin's disease (HD)

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To improve results, in March 1993 we started a pilot study delivering chemotherapy at dose-size and dose-intensity (DI) higher than current regimens, with G-CSF support combined with involved-field radiotherapy (IF-RT). The program utilized cyclic administration of the most effective drugs in HD given sequentially. Epidoxorubicin (EPI), 140 mg/sqm plus vincristine 1.4 mg/sqm day 1 and prednisone 50 mg/sqm day 1–5 was followed by cyclophosphamide (CTX) 4000 mg/sqm on day 15 and by etoposide (VP-16) 2000 mg/sqm on day 29. After a two week interval, the same sequence was recycled once and a final EPI was given on day 85. Four weeks after, IF-RT (30–36 Gy) was started. G-CSF was given from day 6 to 11 after EPI and CTX and from day 3 to 11 after VP16. Fifty untreated consecutive pts, entered as of 1/96, are evaluable. Characteristics were: M/F 23/27; median age 30 yrs (range 17–54); stage IIB 27; III 9; IV 14; B symptoms 43; bulky disease 19; <3/>3 sites 12/38.

After a median follow-up of 27 mos the results were as follows: complete remission (CR) 94%; freedom from progression 72%; overall survival 96%.

Compliance was good; pts completed the drug program within a median of 12.6 weeks and the median DI was 0.95. No cardiac or lung toxicity was detected. Two leukemias developed at 20 and 22 mos. This program was safe and able to induce a high CR rate. However, the percent of pts in continuous CR is superimposable to that achieved with conventional combinations. For this reason the risk/benefit ratio of this intensive regimen seems to be higher compared to standard treatments.

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FISH identifies different types of duplications with 12q13–15 as the commonly involved segment in B-cell lymphoproliferative malignancies characterized by partial trisomy 12

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Partial trisomy 12 was detected in 18 out of 1836 cytogenetically analyzed cases of B-cell NHL and occurred predominantly in clinically progressive chronic lymphocytic leukemia, mixed cell type, and advanced stage follicle center cell lymphoma (FCCL) at the time of relapse or transformation into diffuse large cell lymphoma (DLCL). Partial trisomy 12 consistently included the long arm of chromosome 12, either completely or partially, and resulted from dup(12)(q) or different other rearrangements involving chromosome 12. The duplications were cytogenetically identified as dup(12)(q13q23), dup(12)(q13q22), or dup(12)(q13q15) in FCCL or t(14;18)-positive DLCL; dup(12)(q13q22) or dup(12)(q13q24) in chronic lymphocytic leukemia; and dup(12)(q13q21) in a case of t(14;18)-negative DLCL. FISH using library probes and a panel of YAC probes mapped along the long arm of chromosome 12 confirmed the cytogenetic results in all cases analyzed except for three cases of t(14;18)-positive FCCL or DLCL with dup(12)(q). In these cases, FISH showed similar, possibly identical duplications, which involved a region more centromeric (12q11–q21) than assumed by karyotypic analysis (12q13–22 or 12q13–23). In addition, commonly duplicated regions of chromosome 12 could be defined: 12q11–21 for FCCL or t(14;18)-positive DLCL, 12q13–22 for chronic lymphocytic leukemia, and 12p13–q15 for marginal zone cell lymphoma, all of which overlapped in 12q13–15.

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Clinico-pathological study of the adult Hodgkin's disease. 15-year experience, National Cancer Institute, Cairo, Egypt

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Purpose: This is a 15-year retrospective study of the histologic and clinical