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Natural History of Kaposi's Sarcoma in the Epidemic of Acquired Immune Deficiency Syndrome

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Introduction:

Kaposi's sarcoma (KS) represents an interesting model of virally associated human neoplasms.[1] The disease exhibits multiple unique features in its histopathology and clinical course.[2] KS is a multi-focal, systemic neoplastic process, which is histologically characterized by proliferating fibroblastic and microvascular elements. However, it is unclear whether this disorder is primarily a malignant neoplasm, or whether it represents a reactive phenomenon. Some of the unusual features of this neoplasm include: 1. Cluster distribution in certain endemic areas, such as Zaire, Kenya, Tanzania, Eastern Europe, Italy and North America;[3] 2. Male predominance with a ratio of 10:15 males to one female in Africa and a 3:1 male:female ratio in the United States;[2] 3. Diversity of clinical presentations, from slow growing and indolent tumors, predominating in European and North American populations to the

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fatal lymphadenopathic variant in African children;[2] 4. Occurrence of KS in renal transplant recipients, and patients with immunologic disorders following treatment with immunosuppressive agents;[4,5] 5. Serologic and genetic evidence for close association between KS and cytomegalovirus[6,7]; 6. Increased incidence of second primary cancers in KS patients especially lymphoreticular malignancies;[1] and 7. Marked increase in the incidence of KS in the epidemic of AIDS.[8,9]

Epidemiology:

The unusually high incidence of KS in the epidemic of AIDS has lead the Center for Disease Control (CDC) to classify KS as a diagnostic presentation of AIDS in high-risk populations.[10] KS is reported as the initial manifestation of AIDS in approximately 30% of cases and this percentage has remained fairly constant during the course of the epidemic.[10]

At Memorial Sloan-Kettering Cancer Center, (MSKCC), we have seen more than 200 cases of KS since the beginning of the AIDS epidemic. The mean age of of KS-AIDS at the time of their initial diagnosis is 38 years, with a range of 23-67 years. The majority of KS-AIDS cases have been reported in men; however, women with KS-AIDS have also been seen. In the MSKCC series, there have thus far been only 2 female patients with KS-AIDS, accounting for less than 1% of all cases. This is a skewed population: largely because most KS-AIDS patients referred to MSKCC are homosexual or bisexual men. It would be of great interest to see whether KS-AIDS will show a similar prevalence among men and women in certain geographic areas, such as Haiti or

Africa, where AIDS is reported to be transmitted through heterosexual contact. Preliminary data suggest that the number of KS-AIDS cases among female intravenous drug abusers (IVDA) is very close to those of male IVDA. KS-AIDS has been reported among all risk groups for AIDS including children[11] and hemophiliacs[12]. However, it is seen more frequently among homosexual men. This is believed by some to be related to the increased incidence of CMV infection in homosexual men. It is also reported that KS-AIDS is seen more frequently among those homosexuals who use unlabeled amyl nitrites rather than those who use labeled ones[13]. KS is more often seen among New York and California AIDS cases than among those from other parts of the country. In addition, it is more frequent among whites and homosexuals than black and intravenous drug abusers.[14,15]

The overall mortality rate of KS-AIDS is approximately 41% (Figure 1), with over 60% of cases being alive by one year, and 50% by 22 months of follow-up. The overall survival of KS-AIDS is said to be 18 months. However, there are cases who have already lived 3-4 years and at present are still doing well.

Clinical presentation and course of the disease

As in the case of the classical KS[1,16], the diversity of clinical presentations is one of the main features of KS-AIDS[16]. Such diversity is seen in almost every feature of the disease, including the clinical presentations laboratory findings and the biologic behavior of the tumor.

KS-AIDS is a multicentric neoplastic process which initially

manifests with a single, or more frequently, multiple, pink, red to violaceous macules, papules, and/or nodules on the skin or mucosal surface.[17] The lesions then become darker and larger, and may coalesce to form raised plaques, or tumors. The lesions often appear elongated and oval in shape, and frequently follow the lines of cleavage as seen in pityriasis rosea[18]. In rare occasions, KS-AIDS lesions may manifest as small or large patches of purple-blue discoloration, mimicking ecchymoses. KS-AIDS lesions are frequently located on the trunk, upper extremities and head and neck areas in contrast to the distribution of lesions on the lower extremity in classical KS. The tip of the nose is a common and unique location for KS-AIDS. Lesions on the lower extremities are also seen in KS-AIDS but much less frequently than those of classical KS. Soft tissue infiltrates by KS tumor are also seen in the lower extremities. Involvement of the soft tissues of the head and neck areas, however, is very often seen, and carries with it a poor prognosis. Multiple sites of involvement including mucous membranes, gasterointestinal (GI) tract and lymph nodes, are also characteristics of KS-AIDS. KS-AIDS may also initially manifest only with lesions in the mucous membrane. The hard palate is one of the most common sites, but tumors may infiltrate gingivae, oropharynx and tonsils. Ulceration of the mucosal lesions is more common than in skin lesions. Involvement of the upper and lower GI tract is seen in approximately one third of the patients examined by endoscopy. Early lesions in the GI tract may appear as pink to purple submucosal macules of different sizes. Older lesions may protrude into the muscosal surface and appear as nodules or

tumors. Ulceration and bleeding from the GI tract lesions is infrequently reported in KS-AIDS. Because of the deep location of KS lesions in submucosal areas, biopsies of GI tract lesions which are performed during gastroscopy are very often negative for KS tumor. KS-AIDS has been frequently seen and reported in the lymph node, and there have been cases in which KS-AIDS has remained localized to the lymph node (personal observation). In the MSKCC series, 47% of cases overall had lymph node disease. Histologically, KS tumors are usually seen in the capsular area of the lymph node; however replacement of the entire lymph node has also been seen.

KS lesions are also reported in the lung, liver, pancreas, adrenal gland, spleen and testis.[8,14] At postmortem, KS tumors have been reported to involve almost all internal tissues, except the brain. Patients with KS-AIDS also manifest systemic complaints of fever, weight loss, malaise, anorexia and diarrhea[14,15].

The extent of KS tumors and their biologic behavior may vary considerably. It may manifest as slow-growing and indolent, or rapid and fulminant. In general, the sites of KS-AIDS involvement and the tumor load do not seem to correlate with the prognosis of the disease. In addition, there is no correlation between the initial site of KS tumor and the prognosis. We have seen cases of KS-AIDS with only very few KS lesions in the late stages of the disease. In contrast, there are cases with massive tumor involvement who have prolong survivals, and have responded to treatment rapidly. An attempt has been made to develop a staging classification for KS-AIDS.[19] However, staging of KS

does not at this time seem to have prognostic or therapeutic value. In another small number of the KS-AIDS cases who have small tumor loads, the disease appears to be stable and not progressive after several years of follow up.

Histopathology

Histopatholgic features of KS are characteristic and consist of interweaving bands of spindle cells and vascular structures embedded in a network of reticular and collagen fibers.[2] The vascular component appears mostly as cleft-like spaces or as delicate capillaries. Spindle cells may show a wide range of nuclear pleomorphism in the tumor, and several different histopathologic patterns may be identified. Histologic patterns in KS tumor may vary from lesion to lesion and even in different sections of the same lesion. In early lesions[19,20] dilated vascular channels lined with normal-appearing endothelial cells are present in the upper dermis. When the lining of the vascular spaces lack erythrocytes, a lymphatic-channel-like appearance is seen. Sparse mononuclear infiltrates composed mainly of lymphocytes and plasma cells are observed. Siderophages are not present in early lesions. In the older lesions,[20,21] endothelial cells are more prominent, extravasated red cells and siderophages are seen, and spindle cells with various degree of pleomorphism and atypical it extend in various directions. It is generally accepted that the histologic features of KS-AIDS are indistinguishable from those of classical KS[20,21].

Immunogenetic

Heritage and ethnicity appear to play a role in the development of classical KS.[16] In North America the majority of cases have ancestry going back to eastern Europe or Italy, or are from Ashkenazi Jewish extraction[16]. During the initial phase of the epidemic of AIDS, there was an increased incidence of KS-AIDS among (high-risk) individuals of Jewish or Italian extraction, suggesting a possible role for ethnicity and heritage as susceptibility factors. Later on, however, it became clear that KS-AIDS can occur in persons from any ethnic group or nationality.

Studies of major histocompatibility complex antigens have similarily demonstrated an increase in the frequency of histocompatibility leukocyte antigen (HLA)-DR5 in classic KS[22]. An intial increase in the frequency of HLA-DR5 among KS-AIDS cases with Italian and Jewish extraction and HLA-DR2 in patients with Northern European extraction was observed. [22,23] Present data, however, show that these antigens are no longer seen with increased frequency, and therefore are not currently considered risk factors for KS-AIDS. The reason for this change in the frequency of the HLA class II antigen-association is not as yet known, and requires further study. More recent data from the MSKCC group (unpublished data) demonstrate that HLA-DRW53 is significantly increased in all KS-AIDS populations except in blacks. In addition, an increased frequency of HLA-DRW6 among KS-AIDS-cases with Italian or other Caucasion background is seen. Further studies are needed to clarify the possible role of

HLA-associated susceptibility factors in KS-AIDS.

Laboratory Findings

These abnormal parameters appear to be closely associated with the underlying infection of Human T Lymphotropic virus III (HTLV-3)/Lymphadenopathy Associated Virus (LAV). In classical KS, the major abnormal laboratory findings include: presence of high levels of circulating anti-CMV antibodies[6]; anemia in a very small percentage of cases[16] and a reduced ratio of T helper/T suppressor cells.[24] In cases of KS-AIDS, a considerable number of laboratory parameters are found to be abnormal. These factors may play a major role in the prognosis, response to therapy and the general outcome of the disease. In the MSKCC series of KS-AIDS, a continuous decrease in the number of white blood cells (WBC), absolute numbers of neutrophils and lymphocytes (Safai, et al, unpublished data) has been observed. It has been shown that WBC and absolute lymphocyte counts are closely associated with survival ($p < .05$). By two years from the diagnosis 60% of the patients with normal WBC were alive, as compared to 45% of those with abnormal WBC. Similarly, patients with normal absolute lymphocytes (55% alive by 2 years from diagnosis) survived longer than patients with abnormal values (30% alive by 2 years from diagnosis). The survival distributions for these are shown in Figure 2 and 3.

Among the various laboratory parameters, the absolute number of T helper cells and the ratio of T helper/T suppressor (T_4/T_8)

cells have special significance and have become the hallmark of the disease. This is a result of 1) the almost universal finding in AIDS patients of a lowered number of T_4 cells and T_4/T_8 ratio; and 2) that the etiologic agent causing the epidemic of AIDS, namely HTLV-3/LAV, has a special tropism for T helper cells. In the cases seen at MSKCC, we have observed a continuous and progressive decrease in the absolute number of T_4 cells and T_4/T_8 ratio among the majority of cases. It was observed that as the disease progressed, the number of T_4 cells and the ratio of T_4/T_8 continued to decrease to the end stage of the disease. We have, however, found a small subgroup of KS-AIDS cases who have normal values for these parameters in a 3-4 year follow up period. These cases seem to have a more stable and less aggressive disease. The observations indicate the presence of a spectrum of disease presentations in KS-AIDS.[25] In addition, the data suggest that the abnormal number of T_4 cells or the T_4/T_8 ratio is not a pre-requisite for the development of KS. Thus, the level of immune deficiency needed for this tumor to arise is perhaps not measurable by the presently available laboratory assays. In the cases of classical KS we have also observed a reduction in the ratio of T_4/T_8[24]. However, these lowered values are stable and not progressively decreasing which is a major difference from those of KS-AIDS.

In testing for an association between these variables and an increase in survival both were found to be significant ($P < .05$). Figures 4 and 5 contains the survival distributions for these variables. Patients with 30% or more T_4 cells survived

longer (68% alive by 2 years from diagnosis) than cases with fewer than 30% T_4 cells (44% alive by 2 years from diagnosis). Similarly, patients with T_4/T_8 ratios less than 1.0 had a lower survival rate than patients who had a T_4/T_8 ratio between 1.0 and 1.6, or than those who had a T_4/T_8 of at least 1.7. The proportion alive at 2 years from diagnosis was 43%, 64% and 93% respectively for these three groups. When comparing the number of T_4 cells and the T_4/T_8 ratio in patients with KS-AIDS to high risk controls, it is clear that there is a statistically signficant difference ($P < .05$). The patients had a much lower T_4 cells and T_4/T_8 ratio than the controls.

Functional studies of T cells and B cells in patients with KS-AIDS have indicated a close association between these parameters and the course and prognosis of the disease. Detailed information has been reported previously in this regard[26] In our series of KS-AIDS cases we have demonstrated a general decrease in the functional capacities of the T and B cells in the majority of the cases. The proliferative response to E. coli and Con-A appears to be a more sensitive indicator in this group of patients. By 2 years from diagnosis, 80% of the patients with normal Con-A responsiveness were still alive, compared with only 38% of patients with abnormal Con-A responses surviving. Patients with higher levels of E. coli responsiveness survived longer than patients with lowered levels. Similarly the response to CMV antigens was closely correlated with survival of KS-AIDS patients (Figures 6, 7, 8). However, a small subgroup of KS-AIDS patients have normal proliferative responsiveness to various

T and B cell mitogens. These observations again support the concept that measurable loss of T and B cell functions is not a prerequisite for the development of KS in AIDS victims. Perhaps more subtle alterations in immune competence or a specific loss of immunologic function, is needed to allow the tumor to grow.

Following the discovery of the etiologic agent of the epidemic of AIDS, it has been shown that cases of classical KS are negative for the HTLV-3/LAV (Safai, et al unpublished data). However, nearly all cases of KS-AIDS who have been so far tested have shown antibodies to the HTLV-3/LAV, and the virus has been isolated from most of the cases cultured.[27-32] This information clearly suggests that HTLV-3/LAV is not the etiologic agent of KS but may account for its different biologic behavior in AIDS. In the MSKCC series of KS-AIDS, antibodies to HTLV-3/LAV have been observed. It is of interest to note that the levels of HTLV-3/LAV antibodies decrease as the disease progresses.[25] However, this appears to be unrelated to the progress of the KS tumor. In addition, we have learned that those individuals who have higher levels of antibodies to HTLV-3/LAV, have a better prognosis, both for their KS tumor and for their AIDS (opportunistic infections). In a small subgroup of KS patients we have been unable to demonstrate the presence of HTLV-3/LAV antibodies (Safai, et al unpublished data). These individuals are mostly young men of high risk groups (homosexuals) who have shown either stable KS tumor or have responded well to treatment (interferon). Whether these individuals are suffering from KS-AIDS, or whether they have

developed a classical form of the disease is unclear. Attempts to isolate HTLV-3/LAV from these cases are underway.

Pathogenesis

While KS has been diagnosed in approximately 30% of AIDS victims, the association of this tumor and the HTLV-3/LAV infection is not well understood. It is speculated that immune deficiency might play a role in the development of KS. However, in the MSKCC series we have observed cases of KS-AIDS in whom measurable Immune deficiency or abnormalities of the immune regulation can not be identified. Therefore, it is possible that the immune deficiency which is prerequisite for KS to develop is either segmented and/or not measurable to the available tests. In addition, the majority of AIDS victims (70%) do not develop KS, while they still have severe immune deficiency. Thus it is likely that other factors might be involved in the development of this tumor. In fact, KS is mostly seen in homosexual men, indicating a possible involvement of the life style factors closely associated with homosexuality. For example, a recent investigation reports that homosexuals using unlabeled nitrite inhalants are at higher risk for developing KS than those who use this drug in a labeled form.(13)

In addition to the possible role of immune deficiency, CMV infection and genetic host factors have been speculated to be involved in development of KS. In general, it appears that multiple factors are needed for the KS tumor to develop, and the multiplicity of the presentations of this tumor depends on the

levels at which these factors are influencing tumorogenesis. The final outcome of the disease process appears to be under the influence of all these factors.

An interesting but unanswered question concerns the association of HTLV-3/LAV infection and development of KS, especially when this agent is not the etiologic agent of this tumor in the classical form of KS. Two different hypothesis could be offered: 1) Infection with HTLV-3/LAV acts as the promotor factor for the development of KS, i.e. infected mononuclear cells produce angiogenic factors, which in turn allow the development and proliferation of the involved KS cell, in the presence of other required factors. 2. In the high risk populations for AIDS, the necessary factors for development of KS are present and infection with HTLV-3/LAV provides the final factor, whether a segmental immune deficiency state or the promotor factor. Much work is needed to provide answers for some of these intriguing questions.

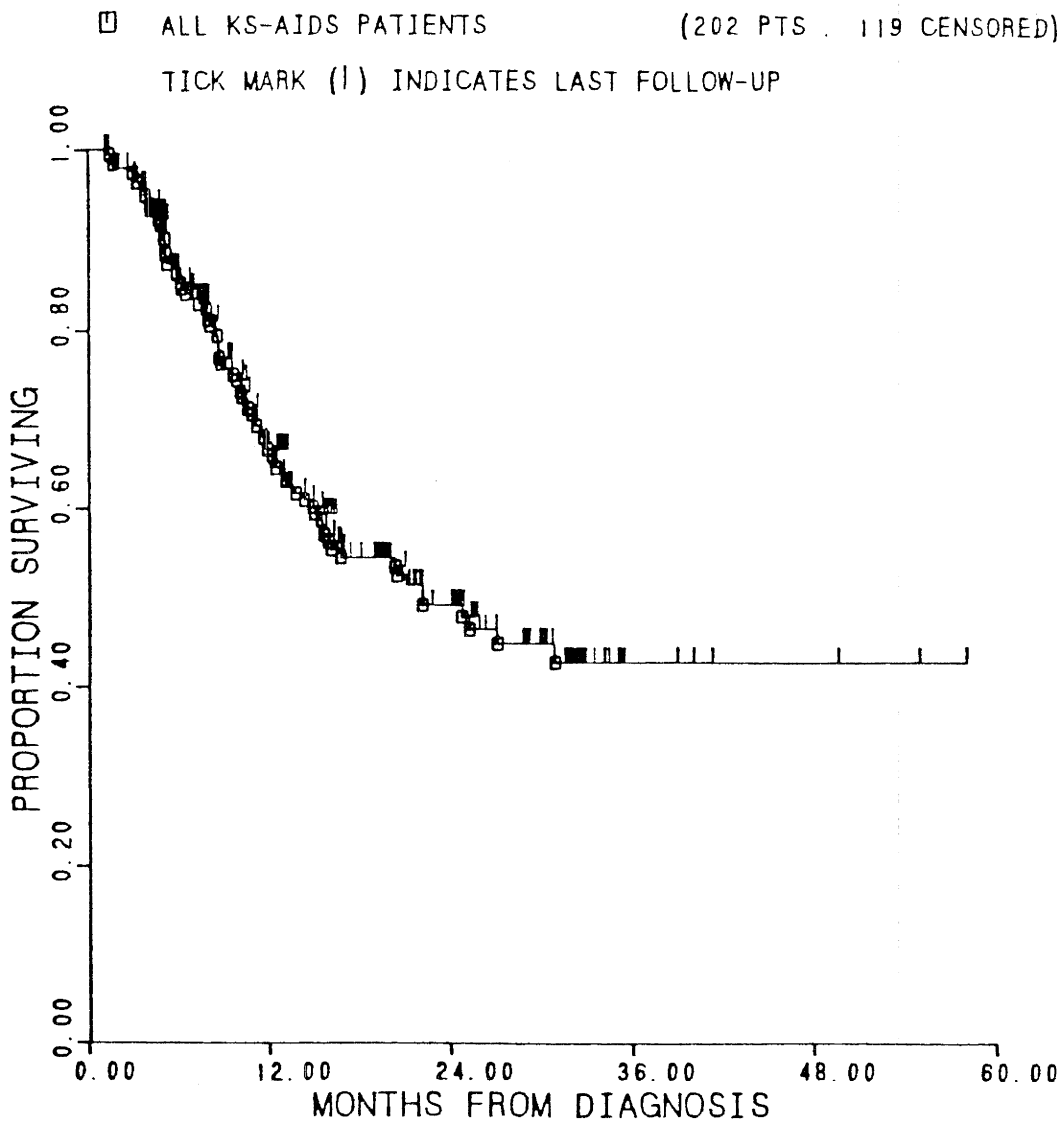

Fig. 1. Survival for all patients with KS-AIDS.

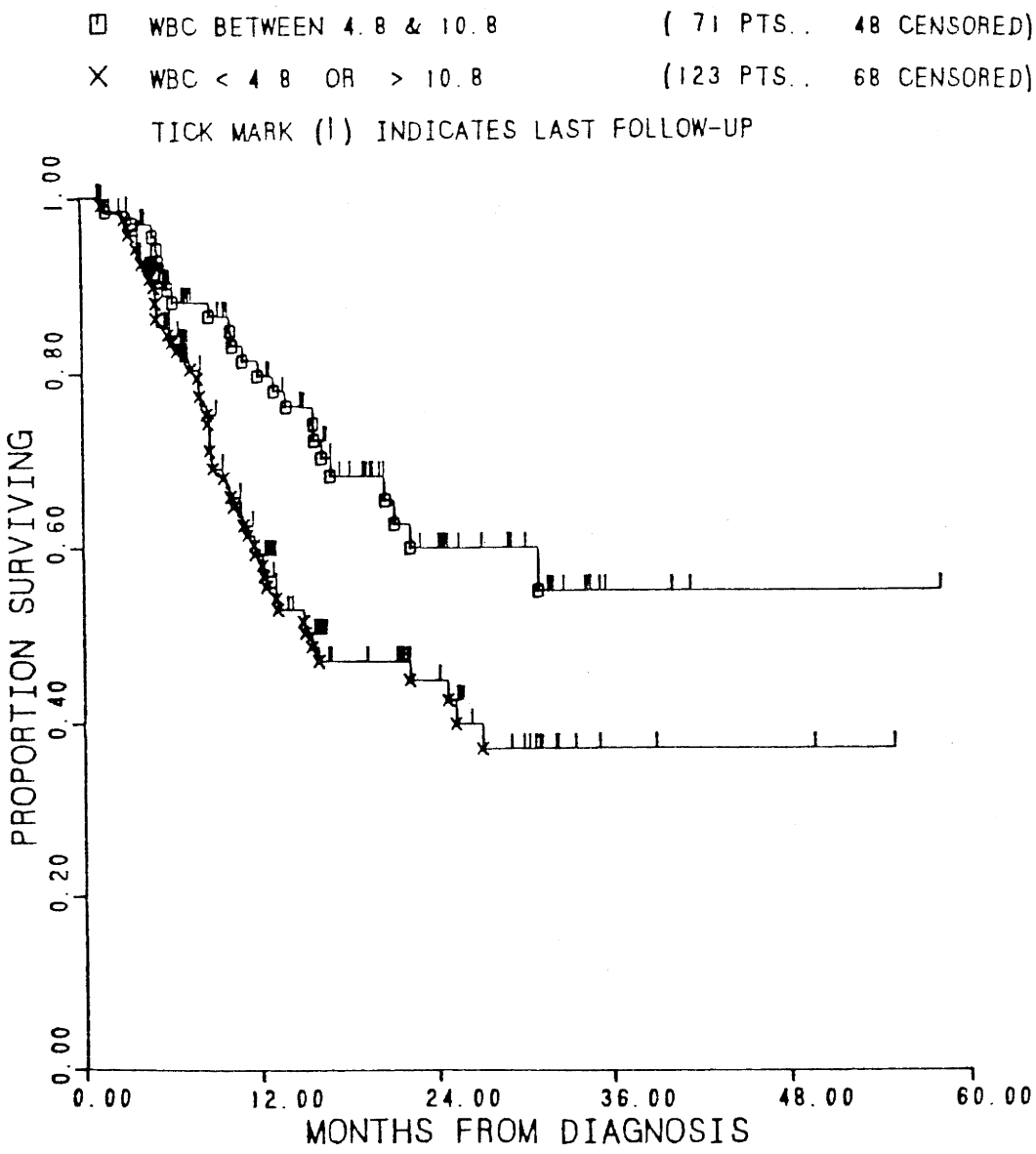

Fig. 2. Survival distributions by initial white blood cell count-normal levels vs abnormal levels.

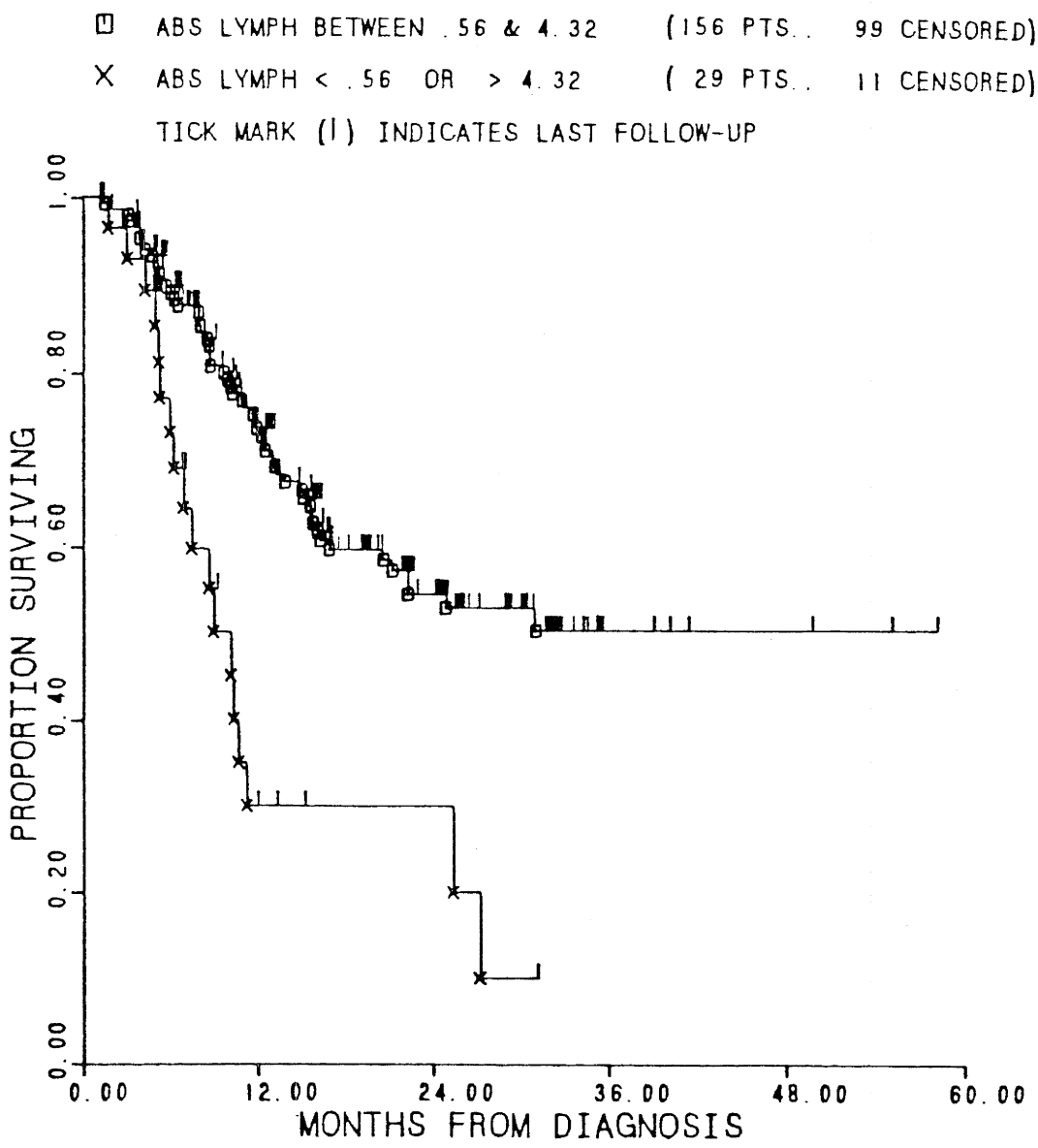

Fig. 3. Survival distributions by absolute lymphocyte count-normal vs abnormal levels.

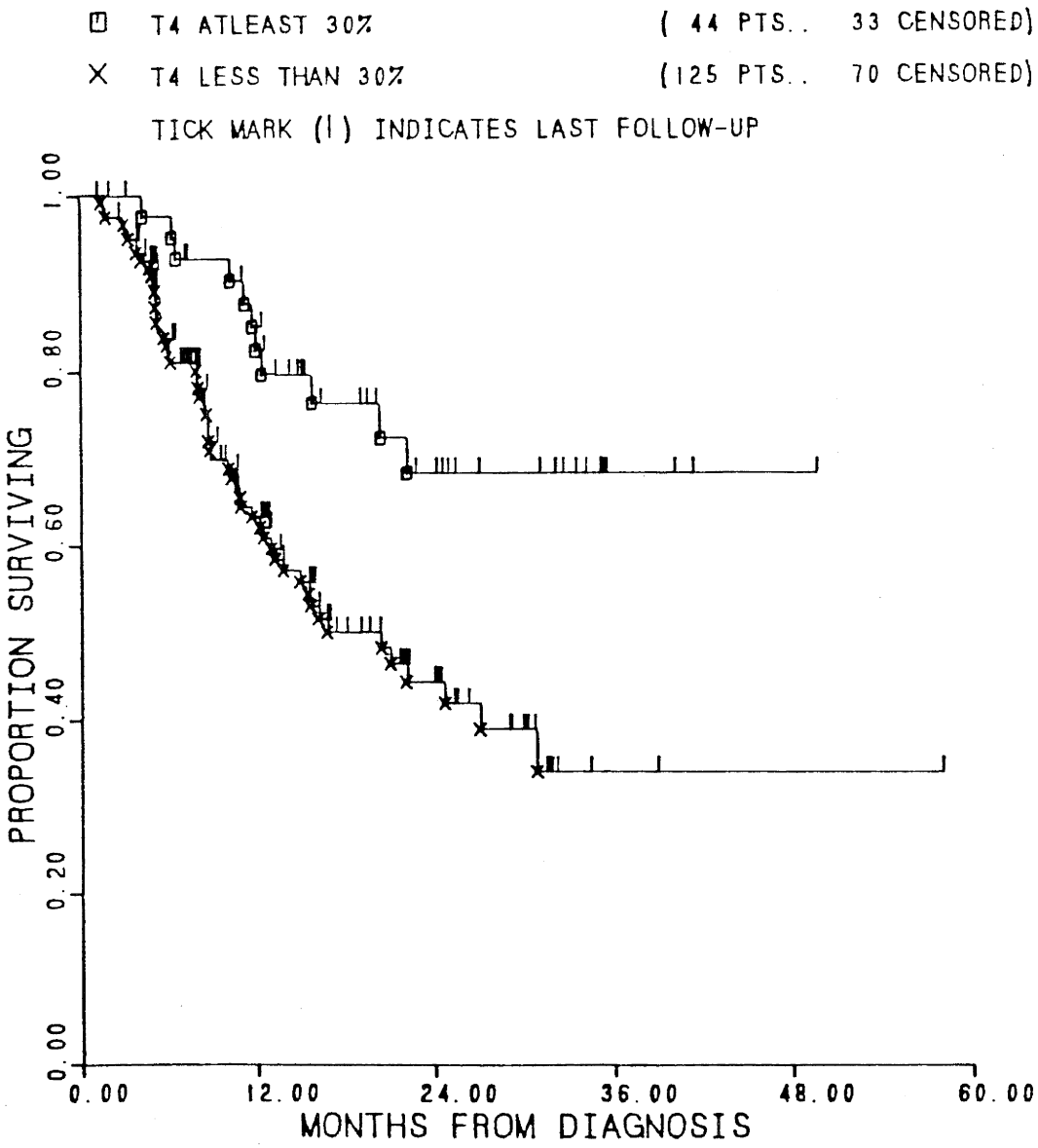

Fig. 4. Survival distributions by percentage initial T_4 cells-at least 30% vs less than 30%.

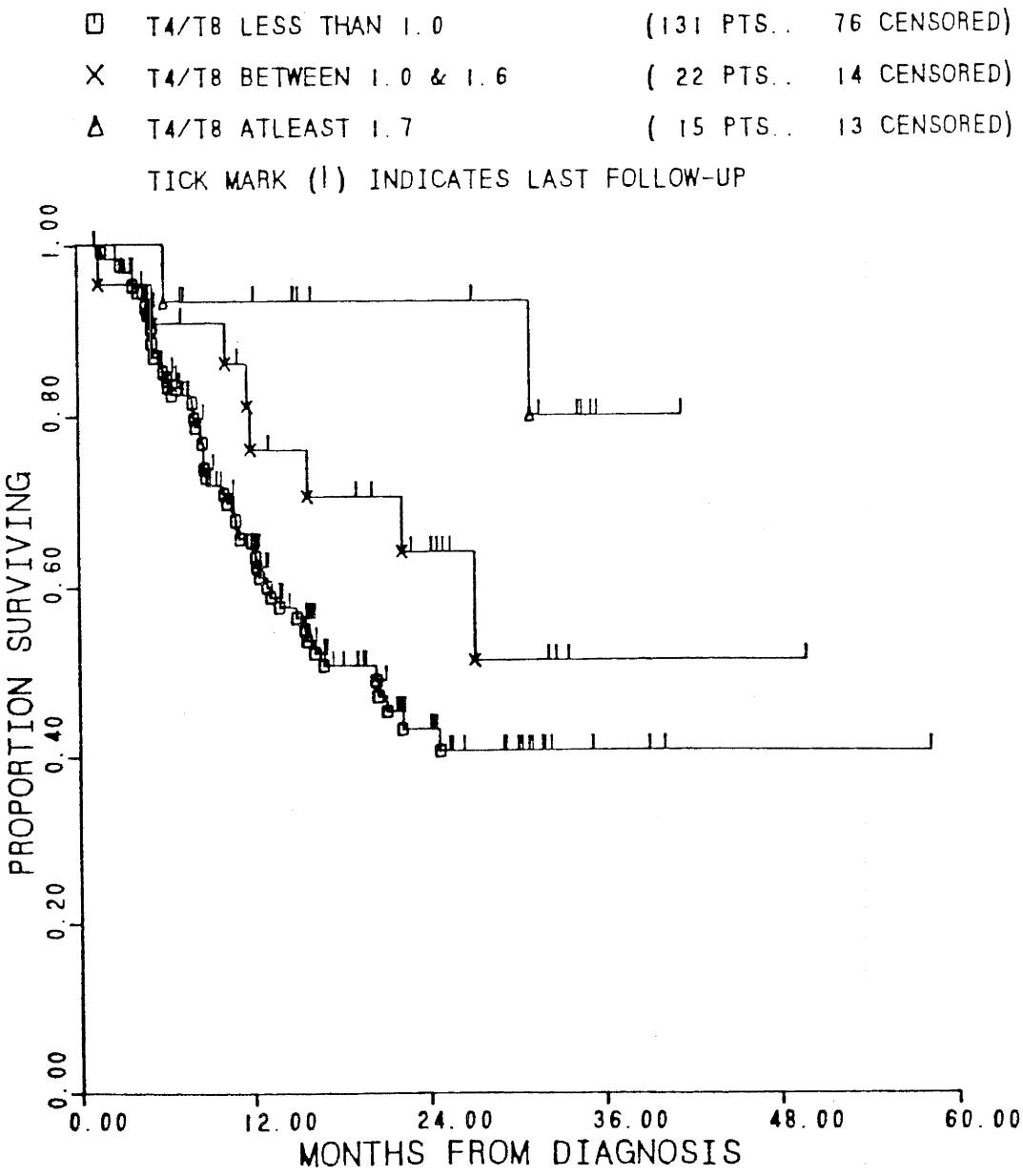

Fig. 5. Survival distributions by initial T_4/T_8 ratio-less than 1.0 vs between 1.0 and 1.6 vs at least 1.7.

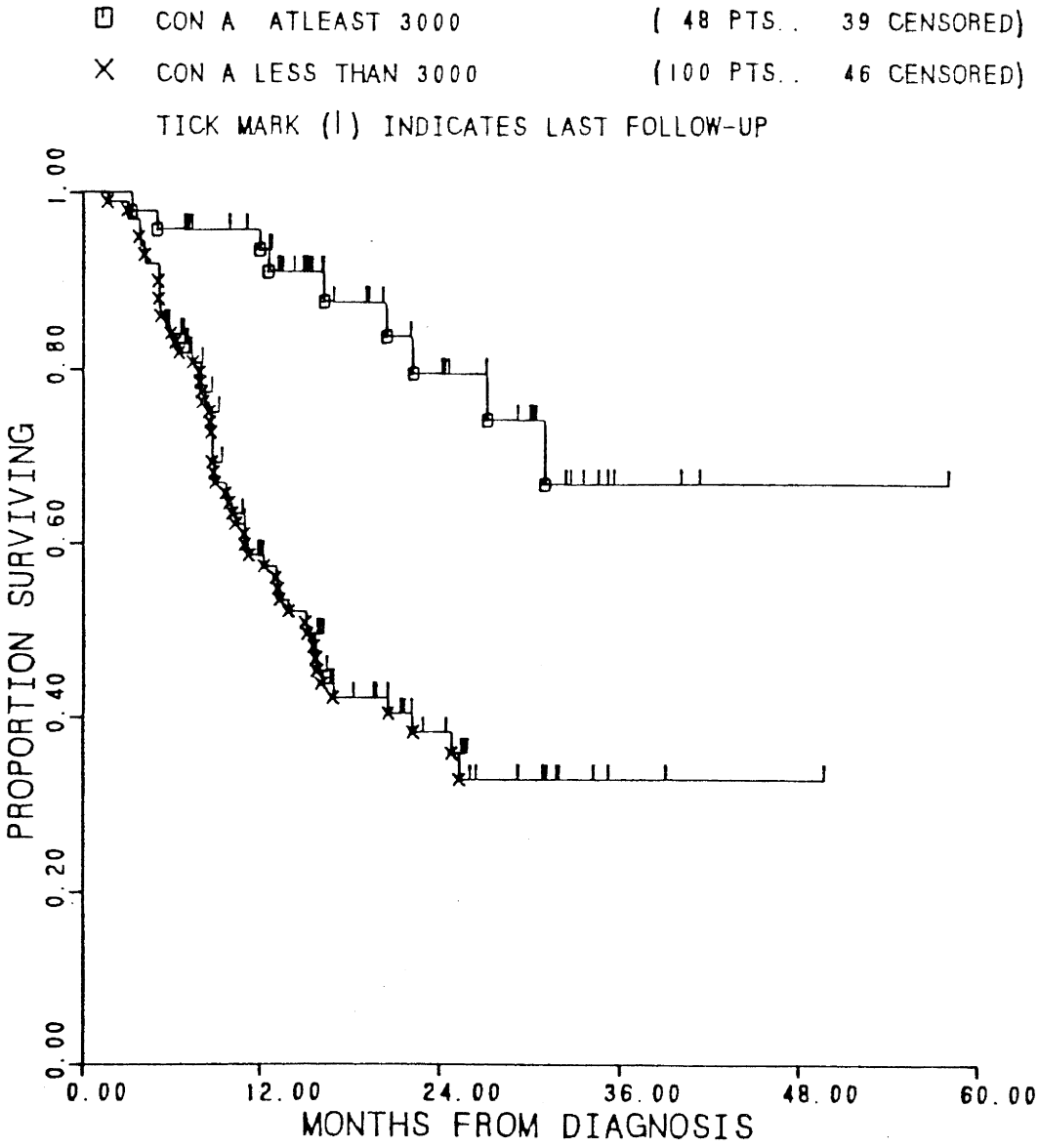

Fig. 6. Survival distributions by initial conconavalin A-normal levels vs abnormal levels.

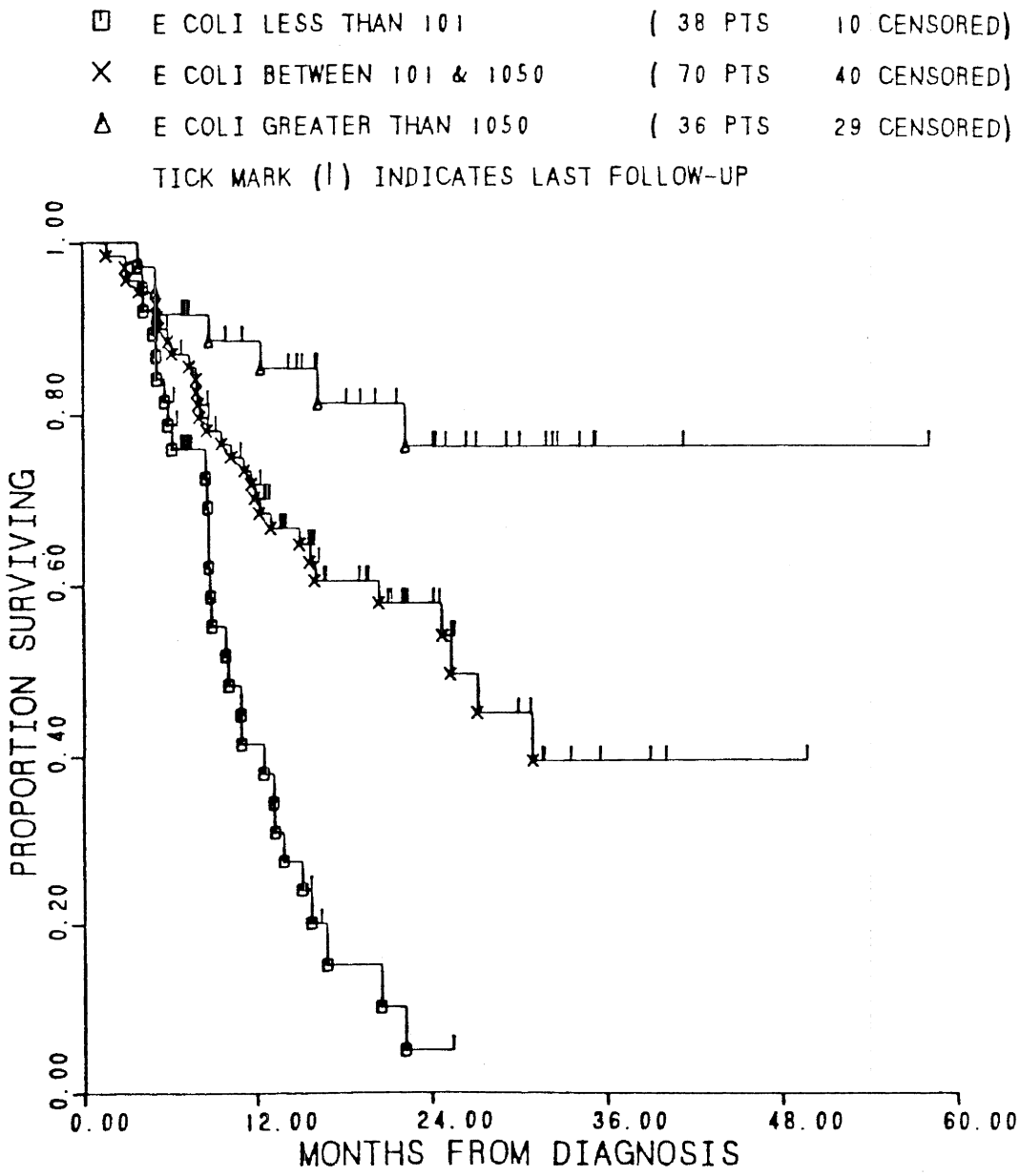

Fig. 7. Survival distributions by initial E. coli-less than 101 vs between 101 and 1050 vs greater than 1050.

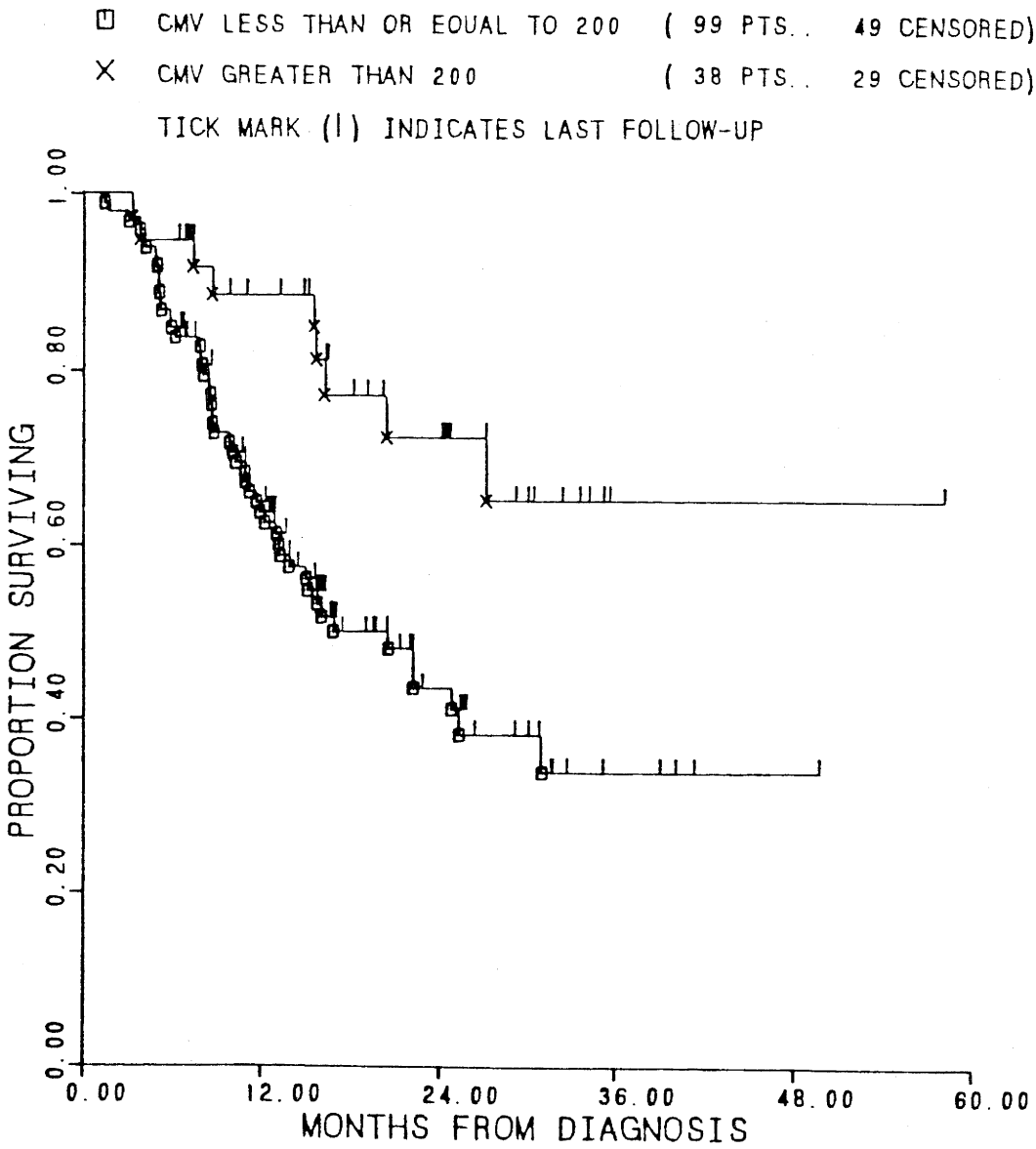

Fig. 8. Survival distributions by initial cytomegalovirus. CMV $\leq$ 200 vs $>$ 200.

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