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A BRITISH NATIONAL LYMPHOMA INVESTIGATION RANDOMISED TRIAL OF SINGLE AGENT CHLORAMBUCIL PLUS RADIOTHERAPY *VERSUS* RADIOTHERAPY ALONE IN LOW GRADE, LOCALISED NON-HODGKINS LYMPHOMA

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Local radiotherapy (RT) alone was compared with radiotherapy plus continuous oral chlorambucil (RT + CHL) for the treatment of localised, low grade non-Hodgkins lymphoma (NHL) in a prospective randomised study of 148 patients. After a maximum of 18 years follow up there was no significant difference in overall survival or disease free survival between the two treatment groups. Age greater than 50 years and low serum albumin at diagnosis correlated with a poor prognosis in the series overall. Over one third of patients with localised, low grade NHL may be cured by RT alone and adiuvant chlorambucil as initial therapy confers no survival advantage.

Key Words: **Chlorambucil, radiotherapy, low-grade non-Hodgkins lymphoma.**

INTRODUCTION

The low grade nonHodgkins lymphomas (NHL) are a histologically heterogeneous group of diseases which account for between 10 and 30% of all NHLs.[1-3] Their clinical course is usually indolent; however, disseminated relapse and transformation to high grade lymphomas are frequent and the commonest cause of eventual death. Clinically staged localised disease (stage I-II) accounts for approximately 25% of all low grade NHLs .[4] Traditionally treatment is with radiotherapy, with between 60% and 70% of patients surviving five years from diagnosis.[5-7] However, disease free survival is shorter and, although cure is possible, it is achieved in a minority of patients.[4]

The use of adjuvant chemotherapy with radiotherapy in localised low grade NHL is controversial. Clinically undetectable disseminated disease may be exposed to treatment with possible delay or prevention of relapse.[6] However, toxicity may be increased, particularly with combination chemotherapy regimens, and overall survival may be unaltered.[8] Furthermore, relapse from low grade lymphomas can occur many years after obtaining remission and the majority of studies reported to date have limited follow up .

In 1974 a prospective, randomised study comparing radiotherapy plus oral chlorambucil versus radiotherapy alone for the treatment of stage I and II low grade NHL was initiated by the BNLI. The long term results, with up to an eighteen year follow up of these patients, are reported.

PATIENTS AND METHODS.

148 patients with localised low grade nonHodgkins lymphoma were recruited between January 1974 and June 1981. All patients were age 15 years or over, gave informed consent, had received no previous chemotherapy or radiotherapy and were free from other known serious disease. Patients were routinely evaluated at presentation with full blood count, liver and renal biochemistry, erythrocyte sedimentation rate, chest X ray and bone marrow trephine. Patients were clinical stage I or II using Ann Arbor criteria to be eligible for the study; staging was confirmed by laparotomy in some patients in whom surgery was performed for diagnostic purposes. Patients with extranodal disease (stages Ie and IIe) were also included. Histological review was performed by the BNLI

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Table 1. *Patient characteristics at entry to the study.*

	RT alone	RT + CHL
Total number patients	82	66
Number of evaluable patients	81 (99%)	65 (98%)
Males/females	44/38	34/32
Median age (range)	60 (30-80)	59 (28-66)
Number <50 yrs (%)	19 (23%)	16 (24%)
Stage I/Ie	35 (43%)	29 (44%)
Stage II/IIe	47 (57%)	37 (56%)
Histology *		
Follicular F1**	46 (56%)	35 (53%)
F2	19 (23%)	19 (29%)
F3	4 (5%)	2 (3%)
Diffuse D1**	5 (6%)	5 (8%)
D2	5 (6%)	4 (2%)
Site (upper/lower) **	38/43	36/28
Stage A/B**	77/4	63/3
Nodal/extranodal	66/16	61/5
Median Hb (g dL^{-1}) +range	13.9 (9.7-17.3)	14.3 (9.5-17.5)
Median ESR (mm h^{-1}) + range	12 (1-116)	7 (165)
Number with ESR >50 (%)	4 (5%)	4 (6%)
Median Albumin (g L^{-1}) + range	42 (27-54)	42 (30-52)
Number with albumin < 36 (%)	3 (4%)	11 (17%)
Median lymphocyte count (x 10^9 L^{-1}) + range.	1.6 (0.35-5.4)	1.9(0.28-12.0)

* BNLI histological classification of low grade nonHodgkins lymphoma. After Bennett J M *et al.* [18]
F1 follicular cells, predominantly small F2 follicular cells, mixed small and large F3 follicular cells, predominantly large
D1 lymphocytic, well differentiated.
D2 lymphocytic, intermediate differentiated
** Some patient data not recorded at randomisation; numbers do not add up to total numbers of patients randomised.

panel according to previously published criteria (9), low grade lymphomas being subclassified as in Table 1.

Randomisation was performed after stratification for sex between local radiotherapy (RT) or radiotherapy plus oral chlorambucil (RT + CHL). Local radiotherapy was given as 3,500 cGy to involved nodes over four weeks. Patients with abdominal disease received 2,500cGy to all nodal areas over four to six weeks. Oral chlorambucil was given as 0.2mg per kg body weight daily for eight weeks, followed by 0.1mg kg^{-1} daily for four months; doses were reduced if cytopenia developed.

Eighty two patients with low grade disease were randomised to receive radiotherapy only (RT) and 66 to receive radiotherapy plus oral chlorambucil (RT + CHL). Patients were randomised before the collaborators histopathology report had been reviewed by the BNLI histopathology panel and the apparent imbalance in the number of patients randomised was due to the exclusion of patients who were considered on review to have high grade disease and were therefore ineligible, or were excluded for other reasons. One patient randomised to receive radiotherapy alone inadvertently received oral chlorambucil with no radiotherapy and one further patient randomised to receive radiotherapy plus chlorambucil was lost to follow up; these patients were evaluated for overall survival only. Patient characteristics in each arm were well balanced with regards to previously described prognostic features (Table 1).

Patients were followed at a minimum of three monthly intervals for one year, then six monthly thereafter. Maximum follow up at the time of

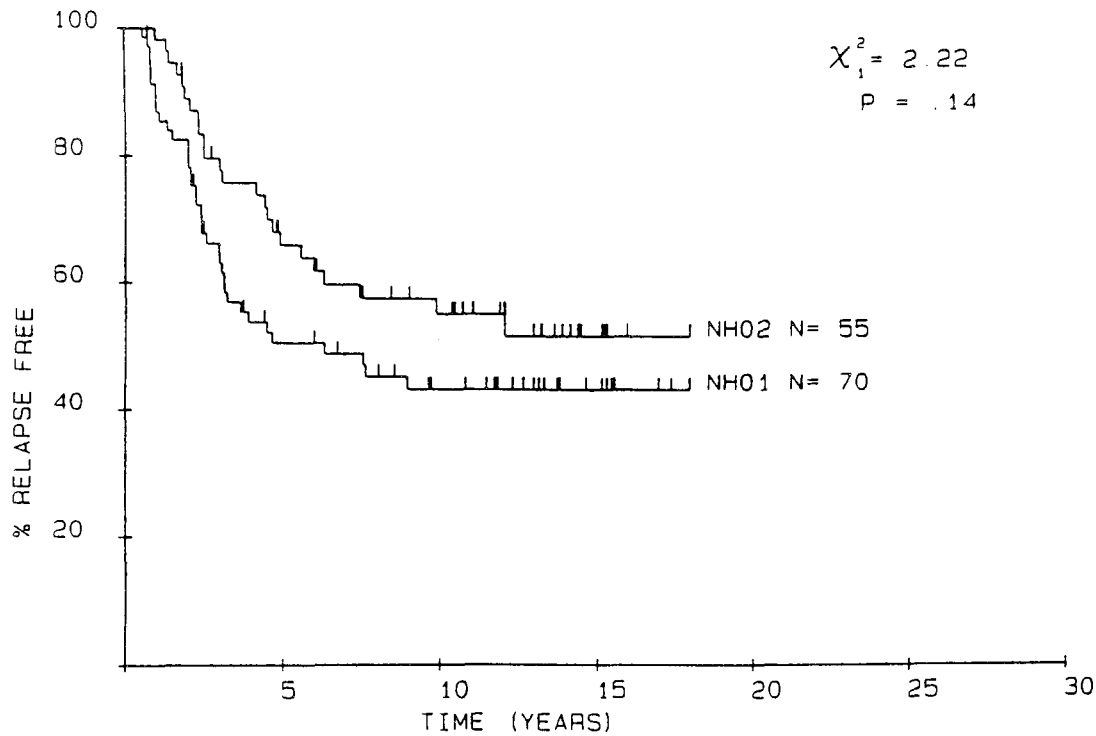

Fig. 1. Relapse rate for evaluable patient~ randomised to receive RT alone (NHO1) or RT+CHL (NH02).

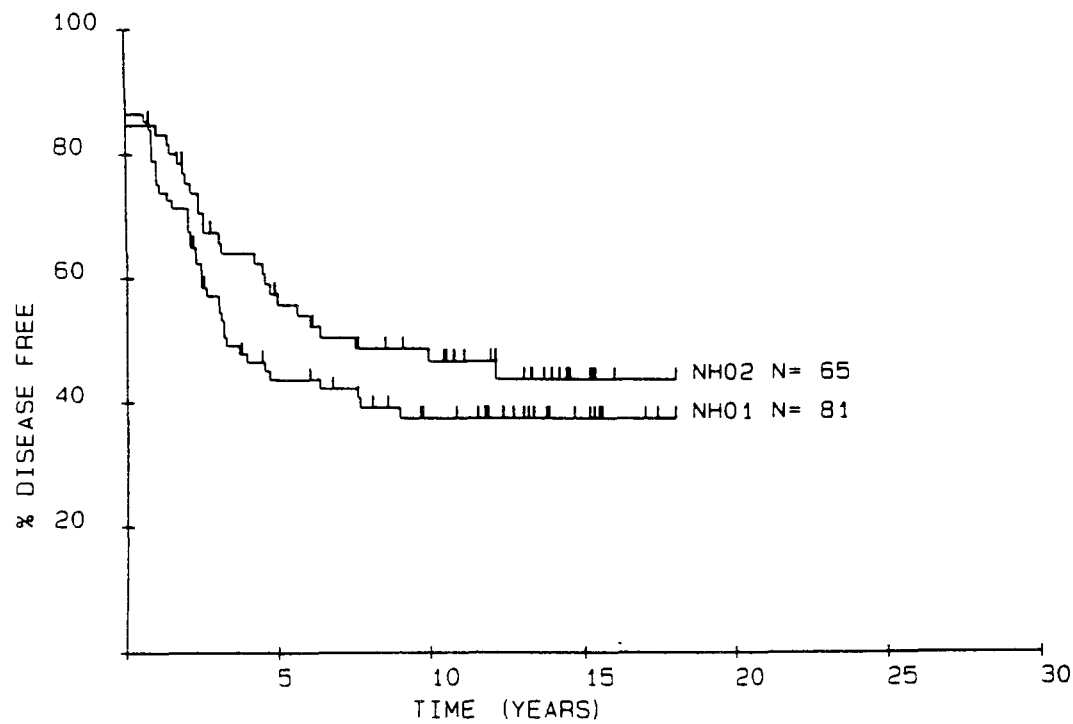

Fig. 2. Overall percentage of evaluable patients achieving CR and remaining disease free thereafter who received RT (NHO1) compared with RT + CHL (NHO2).

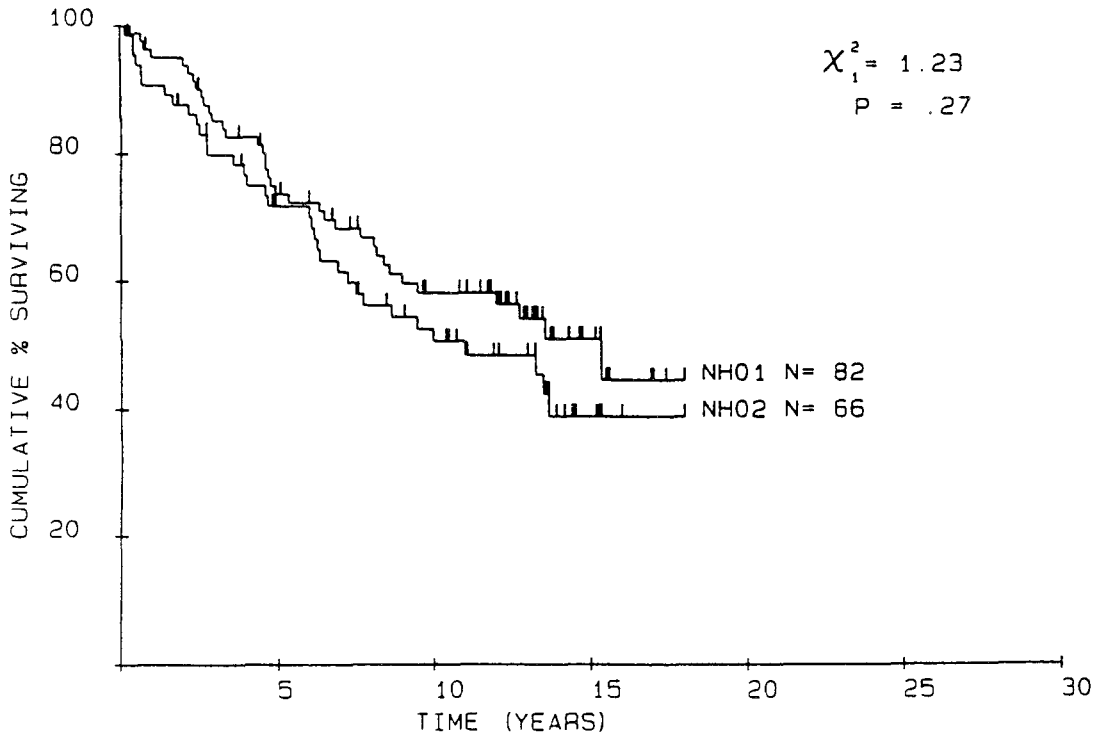

Fig. 3. Cause specific survival from NHL for patients who received RT (NHOl) compared with RT + CHL (NHO2).

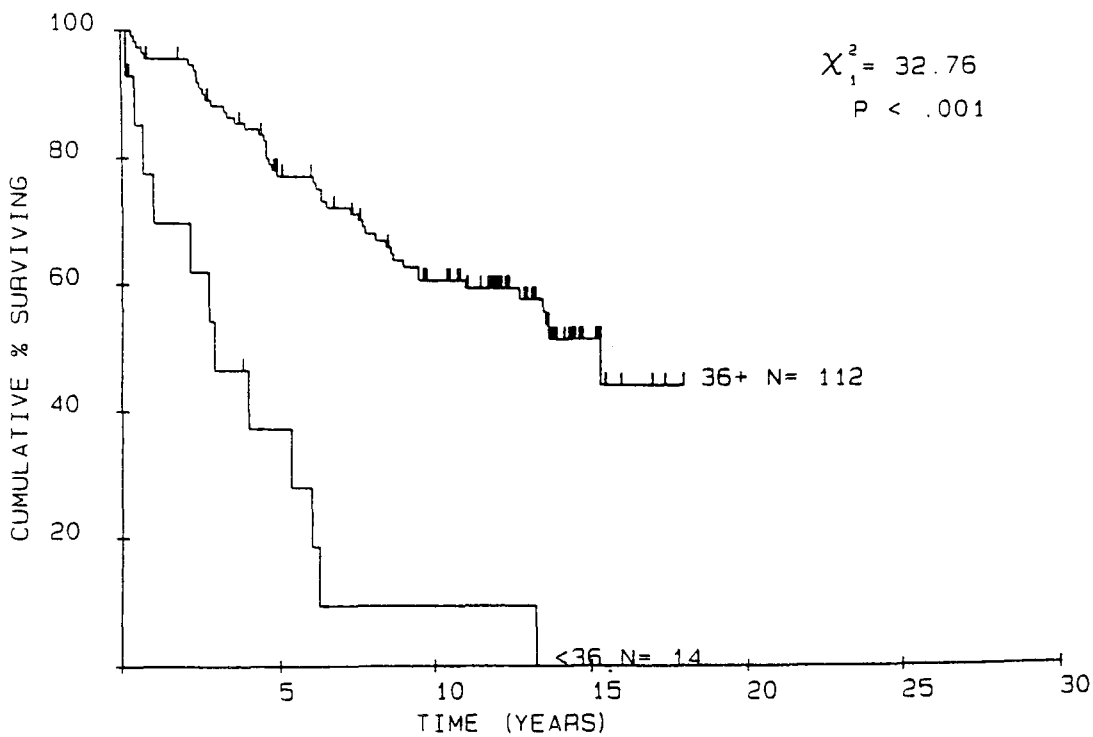

Fig. 4. Cause specific survival from NHL for both treatment groups comparing patients with a presentation albumin of <36 g L^{-1} to those with a level of of 36g L^{-1} or more.

evaluation was 18 years, with all patients having been observed for a minimum of 11 years. Suspected recurrent disease was rebiopsied before further therapy was commenced.

Statistical analysis.

Statistical curves were calculated using the life Table method and statistical comparison of curves was carried out by the log rank test (10). Multivariate analysis was performed by use of the a stepwise proportional hazards model due to Cox.[11]

RESULTS

Survival and relapse

The complete remission rates resulting from initial treatment with RT and RT+CHL were 86% and 85% respectively. There was no significant difference between the two treatments for relapse rate ($p>0.1$), relapse-free survival ($p>0.2$), overall survival ($p>O.1$) or cause specific survival from NHL ($p>0.2$). The relapse rates of those patients who achieved complete remission were 55% and 43% at 10 years respectively, and their relapse-free survivals at this time were 33% and 42%. The overall percentages of patients remaining free from disease solely as a result of their initial treatment were 37% and 46% at ten years, and 37% and 43% at 15 years; the overall disease free survivals at 10 years were 28% and 36% respectively. The overall survivals of the two groups at 10 years were respectively 52% and 42%; the overall cause specific survivals from NHL were 58% and 53% at 10 years and 51% and 39% at 15 years.

The relapse rates, percentages of patients remaining disease free solely from initial treatment, and causespecific survivals from NHL for the two groups are shown in Figs 1-3.

Second line therapy

Forty eight patients received second line therapy for relapsed disease after RT of which 26 (54%) received chemotherapy (either single agent chlorambucil or combination therapy), 19 (40%) received further radiotherapy and three (6%) a combination of modalities. Of 24 patients treated for relapse following RT + CHL 17 (71%) received further radiotherapy, five (21%) chemotherapy and two (8%) underwent surgery.

Prognostic factors

Multivariate analysis was performed on the series overall. The variables included were age, sex, stage,

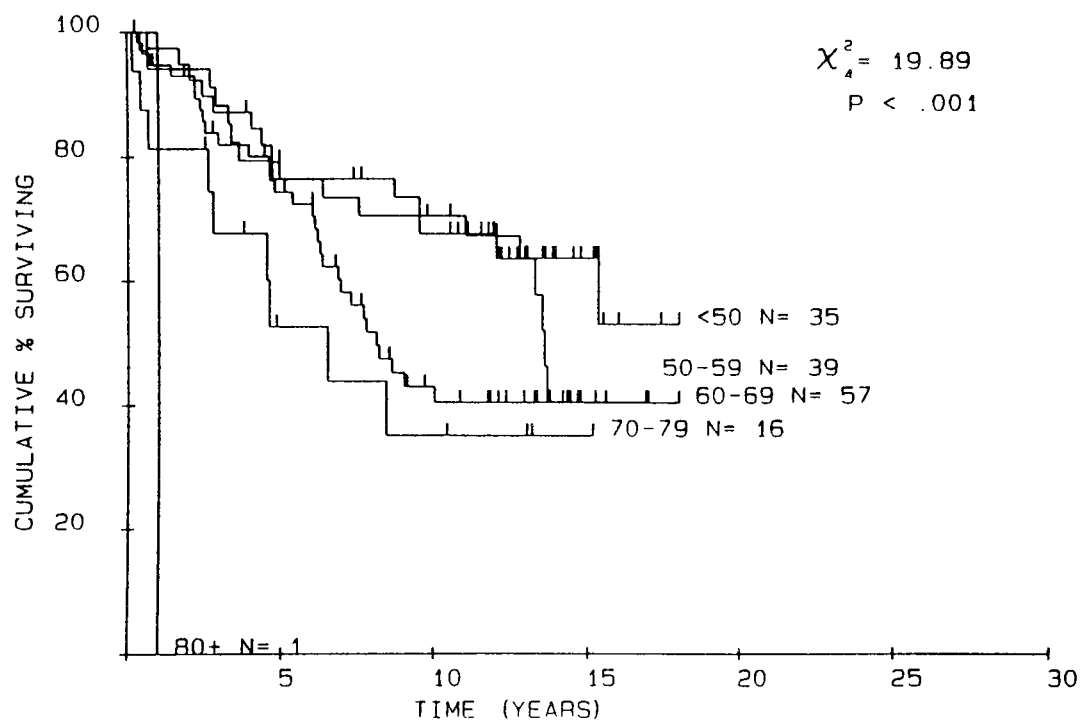

Fig. 5. Cause specific survival from NHL in both treatment groups comparing patients of different ages at presentation.

initial treatment, site of involvement (nodal/ extranodal), histology, systemic symptoms, and albumin, lymphocyte, ESR and haemoglobin levels at presentation.

No variables were found to be prognostically significant for relapse rate. For overall survival, albumin level ($p<0.0001$) and age ($p<0.008$) were found to be prognostically significant, patients with low albumin levels and of older age having a poor survival (Figs 4 and 5).

Secondary malignancy and deaths.

Relapsed or refractory lymphoma was the direct cause of death or significantly contributed to it in 36 of the 46 deaths of patients who received RT alone as initial treatment and in 35 of the 46 deaths of patients who received RT + CHL. Two patients in each group developed high grade lymphoma.

There were 12 second malignancies in the series, five in patients who received initial RT and seven in those who received initial RT+CHL. These comprised 10 solid tumours, one acute myeloid leukaemia and one acute lymphoblastic leukaemia. The solid tumours consisted of three tumours of the prostate, four of the colon or caecum, one of breast, one of oesophagus, and one of pancreas.

DISCUSSION.

The use of adjuvant chemotherapy with radiotherapy for the treatment of localised lymphoma is controversial. Paryani *et al.* (12) demonstrated no benefit from adjuvant chemotherapy for initial treatment of localised follicular NHL. Other studies have shown improved relapsed free survival from concurrent use of combination chemotherapy in low grade NHL but this has not resulted in improved overall survival.[5,6,8] McLaughlin *et al.*[13] have reported improved survival and cure using radiotherapy plus combination chemotherapy for low grade NHL compared with historical controls treated with involved field RT alone.

In the present study, with maximum follow up of 18 years, the relapse rate after initial therapy was less with adjuvant chlorambucil than without, but the difference was not statistically significant and did not result in improved survival. Complete remission and survival rates following both treatment modalities compared favourably with previous studies[5,14,15] with long term disease free survival at 15 years around 30% and cause specific survival from NHL around 40%.

No significant difference in response to the two treatment groups was seen for stage I compared with stage II disease or for low grade lymphoma of follicular compared with diffuse histology. It has previously been suggested that patients with stage II disease at presentation have a higher relapse rate and justify adjuvant chemotherapy.[5,16] Our data suggests that, if this is the case, oral chlorambucil alone is not sufficient to make a difference in this context.

Presentation serum albumin level and age were significantly correlated with outcome, as previously described.[17-21] The population was relatively elderly, and whilst the survival of patients aged <50 was relatively high, that of those aged 60 or more at presentation was relatively poor, particularly for patients with stage 2 disease. This suggests that alternative therapeutic approaches, possibly with more aggressive chemotherapy but with minimal toxicity, may be appropriate for older patients.

There is historical evidence to suggest that chemotherapy does little to alter the clinical course of low grade lymphoma.[4] In addition, radiotherapy combined with chemotherapy has been shown to be no better than chemotherapy alone for stage III-IV low grade NHL.[22] Although clinically localised disease may be truly disseminated at presentation it may not be possible to improve survival by adjuvant use of currently available chemotherapeutic agents. Nevertheless, as demonstrated most deaths in patients with low grade NHL are related to refractory or relapsed disease. Improved survival will only be obtained from better antitumour activity.

Local radiotherapy remains the initial treatment of choice for younger patients with localised, low grade NHL. A significant proportion of patients may be cured by this approach. This study provides no support for the use of firstline adjuvant chemotherapy, particularly in younger patients who may be perceived as being better able to tolerate it.

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