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LATE TOXICITY OF RADIOTHERAPY IN HODGKIN'S DISEASE

The role of fraction size

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Abstract

From 1972 to 1976 patients at the Gustave Roussy Institute were irradiated for Hodgkin's disease using a modified fractionation schedule (3 fractions of 3.3 Gy per week) for operational reasons. From 1964 to 1971 and from 1977 to 1981, a more conventional regimen (4 fractions of 2.5 Gy per week) was used. The rates of the late complications in these two subsets of patients treated with different fractionation schedules at the same total dose of 40 Gy during the same overall time were compared. Mediastinitis was observed in 19% of the '4×2.5 Gy/week' group versus 56% in the '3×3.3 Gy/week' group. Pericarditis in 0% versus 9%, gastroduodenal ulceration and severe gastritis in 10 versus 21% and small bowel obstruction in 5 versus 8%. When using the linear quadratic model with an α/β of 2.5 Gy to evaluate the equivalent dose of 40 Gy given in 12 fractions of 3.3 Gy when delivered by fractions of 2.5 Gy, a value of 46.6 Gy is found. This difference of 6.6 Gy in the equivalent doses (for late toxicity) is likely to account for the significant increase of late radiation injuries, such as mediastinitis and pericarditis, in the present study. The local relapse rate was found to be slightly lower in the 3×3.3 Gy group. However, this possible benefit cannot offset the considerable increase of late complications.

Key words: Radiobiology, fractionation studies; Hodgkin's disease, conventional versus large fractions, late complication.

Hodgkin's disease is a particularly useful 'model' for analysis of late complications after radiotherapy. Since the present treatments are highly effective, a large number of patients can be evaluated during long periods of follow-up. On the other hand, due to the pioneering work of PETERS (12) and KAPLAN (8), radiotherapy for Hodgkin's disease is now fairly standardized; most centres throughout the world delivering about the same radiation dose to approximately the same volumes.

Since about 85–90% of the patients now can be cured from early stages of Hodgkin's disease (8, 16, 17) the problem of late toxicity of the various treatment modalities is becoming predominant. At least for the limited stages, the radiotherapist's energy is presently devoted to the task of obtaining not only cure of the disease, but also as low a rate as possible of late complications (16, 17).

In relation to late complications of radiotherapy, attention has recently been drawn to the role of fraction size. Data in the literature suggest that any increase in the fraction size above 2–2.5 Gy leads to a greater risk of late complications (6, 9, 11, 19, 20).

At the Institut Gustave Roussy (IGR) at Villejuif, we have had the opportunity to compare two groups of patients treated for Hodgkin's disease with 2 different fraction sizes, with hardly any variation of the other irradiation parameters. From 1964 to 1972, all the patients were treated using a scheme of 4 fractions of 2.5 Gy per week. In 1972, this schedule was altered to only 3 fractions of 3.3 Gy per week, because of our large number of patients and an insufficient number of therapy machines in our institute. Clinical and radiobiological data concerning the late toxicity possibly related to schedules with reduced fractionation were lacking at that time. From 1972 to 1976, all the patients with Hodgkin's disease were therefore irradiated using this 3×3.3 Gy/week modified technique. In 1976, an increase in the late complication rate was suspected (1, 3, 6), and this technique was immediately abandoned. Since then, Hodgkin's disease has been treated at the Institut Gustave Roussy using 4 weekly fractions of 2.5 Gy (and recently 5 fractions of 2 Gy per week).

In this paper, we shall compare the late complication rates in the two 4×2.5 Gy and 3×3.3 Gy per week fractionation regimens.

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Material and Methods

Selection of patients

All the patients presenting with supra-diaphragmatic stage I and II Hodgkin's disease, who were included by the Gustave Roussy Institute in the 3 successive trials of the European Organization for Research and Treatment of Cancer (EORTC) H1, H2 and H5 were considered eligible for this study.

The first EORTC randomized trial H1 (15) which was conducted from 1964 to 1971, compared regional radiotherapy (RT) alone (mostly mantle field irradiation) with the same RT followed by single agent chemotherapy (CT) (weekly vinblastine for two years). Two hundred and eighty-eight patients were included in the study, thereof 67 from IGR. Of these, 4 were infradiaphragmatic, since in this early trial infradiaphragmatic presentations could be included. Thus 63 patients from IGR could be taken into account.

The second EORTC randomized trial H2 (14) was conducted from 1972 to 1976. It was only designed for supradiaphragmatic clinical stages (CS) I and II. The patients were randomized to undergo laparotomy (and splenectomy) or splenic irradiation. Regardless of the results of the laparotomy, all patients received the same treatment: mantle field followed by paraaortic lymph node irradiation. Moreover, patients with mixed cellularity or lymphocytic depleted histologic types were randomly assigned to receive CT, i.e. weekly vinblastine for 2 years, or a combination of vinblastine and procarbazine for 2 years; 300 patients were registered in the trial. Of these, 69 were from IGR.

The third EORTC trial H5 started in 1977 and ended in 1981. This study was designed on the basis of the H1 data and on the preliminary results of the H2 trial. Favourable and unfavourable prognostic indicators (17) were used to delineate two subgroups out of the supradiaphragmatic CS I and II patients: a 'favourable' group for which RT alone could be sufficient, and an 'unfavourable' group for which more extensive treatment was thought to be necessary. In the 'favourable' group, all the patients underwent staging laparotomy. They remained in this group only if the infradiaphragmatic findings at laparotomy were negative. They were then randomized to receive either a mantle field alone or a mantle field plus paraaortic irradiation.

Patients in the 'unfavourable' group and those in the 'favourable' group with positive laparotomy were randomized to receive either a combined chemotherapy-radiotherapy treatment (3 MOPP-mantle field RT—3 MOPP) or a subtotal (STNI) or total nodal irradiation (TNI); 494 patients were enrolled in this H5 trial, 103 from IGR (16).

The detailed results of these 3 EORTC trials have already been reported (14–17) and will not be considered here in details. The design of the 3 consecutive H1, H2 and H5 trials is shown on Table 1.

By pooling all the patients included in these trials by IGR we registered 235 patients with supradiaphragmatic CS I–II Hodgkin's disease.

Since the aim of the present study was the assessment of the role of fraction size in the late complication rate, we felt it important to avoid large variations in the main irradiation parameters, namely total dose and duration of the radiotherapy. We therefore only took into account the patients who had received between 39 and 41 Gy in less than 35 days either for supradiaphragmatic or infradiaphragmatic irradiation. This selection reduced the number of patients to be analysed, but allowed a precise evaluation of the role of fraction size, since the other main parameters were kept constant.

Consequently, the total number of patients included in the present study is for supradiaphragmatic irradiation 140 (28 (H1 trial) + 48 (H2 trial) + 64 (H5 trial)). Eighty-six patients were treated using 4 fractions of 2.5 Gy per week to a total dose of 39–41 Gy; 54 received 3 fractions of 3.3 Gy per week to the same total dose.

For infradiaphragmatic irradiation, only patients in the H2 and some of the patients in the H5 trial could be taken into account (no infradiaphragmatic RT was planned in the H1 trial—Table 1).

One hundred patients (57 patients from H2 trial + 43 patients from H5 trial) were eligible for the infradiaphragmatic irradiation analysis. Sixty-two were treated using 4 fractions of 2.5 Gy per week to a total dose of 39–41 Gy; 38 received 3 fractions of 3.3 Gy per week to the same total dose.

In the whole group of 140 patients, the mean age was 30 years (SD 10 years), the M/F sex ratio was 1.3. One hundred and four patients received irradiation alone and 36 a combination of chemotherapy and radiotherapy. The subgroup of patients who had infradiaphragmatic irradiation does not significantly differ from the overall group with respect to age, sex and chemotherapy treatment. Out of those 100 patients who were given an abdominal irradiation, 46 previously had undergone staging laparotomy.

Treatment modalities

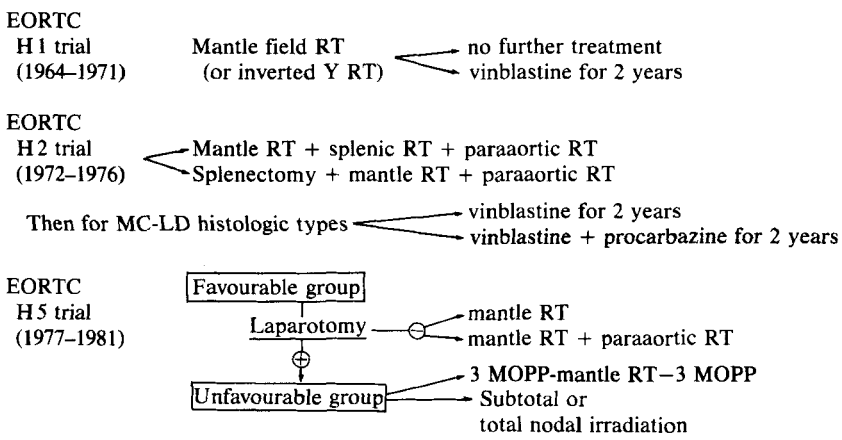
Only the patients included in the H1 trial (28 cases in this study) were treated using Cobalt-60 gamma photons. All the other patients in this series were treated by 25 MV photons from a linear accelerator (Sagittaire CGR).

The supradiaphragmatic irradiation was always a classical mantle, as defined by KAPLAN (8). Thus all patients received irradiation of the mediastinum (lower limit: intervertebral disc T10–T11), and the supraclavicular, cervical and axillary lymph node areas.

The patients who were given infradiaphragmatic irradiation received either paraaortic RT alone, or paraaortic + splenic RT, or inverted Y irradiation (including spleen +/− inguinal lymph nodes) according to the trials to which they were assigned (Table 1). The limits for these volumes were those described by KAPLAN (8). The upper

Table 1

Design of the three consecutive EORTC trials H1, H2 and H5 for Hodgkin's disease stage I–II



limit of the infradiaphragmatic irradiation was calculated for each patient in order to obtain an exact junction of the 50% isodoses of both supra- and infradiaphragmatic RT at midplane of the patient.

The dose was calculated in the midplane on the axis of the beams according to the recommendations of ICRU (7). We previously specified that only the patients who received between 39 and 41 Gy were eligible for the study. The duration of irradiation was usually 28 days. Only the patients who received the previously defined dose in less than 35 days were analysed. Two beams, anterior and posterior, were utilized irrespective of the volume irradiated. Only one beam was used at each session due to the large number of patients to be treated. With the dose calculated at middepth on the central axis, the extreme variations within the treatment volume were 120% and 80% of the prescribed dose per fraction with 25 MV photons in a 20 cm thick patient. Computation with an α/β of 2.5 Gy, for 3.3 Gy per fraction, shows that the increase of the equivalent dose, compared with the technique using two beams per fraction, is approximately 1%. In all patients, half the dose (20 Gy) was given by the anterior, and half (20 Gy) by the posterior portal. The 28 H1 trial patients were treated supine for the anterior beam and prone for the posterior one. All the other patients were treated supine by both the anterior and posterior portals, usually with a skin source distance (SSD) of 110 cm.

The chemotherapy regimens are mentioned in Table 1. Precise details and overall results of these regimens have already been published (14–17).

Characterization of the late complications

In this study, we have only considered the late toxicity of irradiation. For supradiaphragmatic RT, we have studied the rate of radiological mediastinitis as reported by our radiologists on chest radiograms taken during follow-up. We have not used any scoring system for mediastinitis. We have also assessed post-radiation pericarditis, irrespective of the presentation of this complication. Minor asymptomatic pericardial effusions (only detected by chest radiography, ECG or echography) have been taken into account as well as symptomatic severe pericarditis. The analysis of IGR data has already been partly reported (2). We have not considered other late supradiaphragmatic complications.

After infradiaphragmatic irradiation, we have noted the combined incidence of gastroduodenal ulceration and severe gastritis confirmed by endoscopy. In addition, we have assessed the frequency of small bowel obstruction (early post-surgical obstruction, obviously directly related to surgery, were excluded from the study). Part of the data on infradiaphragmatic complications have already been reported (6).

A few cases of myelitis were observed in this series, but they were all found to be related to an erroneous junction of the supra- and infradiaphragmatic fields (at the T10–T11 level). Thus no possible relationship with fractionation could be demonstrated.

We have also excluded the late complications which followed salvage treatment for relapsed Hodgkin's disease, since it was impossible to identify the relative contributions of primary and salvage treatment to complication occurrence.

Statistical considerations

For the analysis we have used a specific statistical data base management system developed at the IGR (18). Data were prospectively stored and abstracted from the files for this study. For statistical comparisons we have used the Fisher exact test. The 95% confidence limits of the proportions p observed were obtained assuming the binomial distribution for p. The Cox's proportional hazards model has been used to assess the prognostic value of the number of fractions on the risk of relapse in an irradiated area, after adjustment for the following characteristics:

Table 2

Late irradiation toxicity as a function of fraction size

	Complication rate		p value
	4×2.5 Gy/week	3×3.3 Gy/week	
Mediastinitis	19% (16/86)	56% (30/54)	<0.001
Pericarditis	0% (0/86)	9% (5/54)	<0.01
Gastro-duodenal ulceration or severe gastritis	10% (6/62)	21% (8/38)	0.11
Small bowel obstruction	5% (3/62)	8% (3/38)	0.53

age, sex, erythrocyte sedimentation rate (ESR), B symptoms, mediastinal involvement, number of initial lymph node areas involved, histological type and treatment (i.e. mantle field ± chemotherapy, STNI ± chemotherapy or TNI).

Results

We will not report here the relapse-free survival and overall survival of the 3 EORTC trials since these have already been published in details (14–17), but concentrate on the complication rates as a function of fraction size (irrespective of the elapsed time of occurrence from treatment completion), and on the other parameters which were found to play a significant role. We will also mention the risk of in-field relapse in the 2 groups.

The overall complication rates in the present series were: mediastinitis: 46/140 (33%, with 95% confidence limits (c.l.) 25–41%); pericarditis 5/140 (4%, c.l. 1–8%); gastroduodenal ulceration or severe gastritis (1 patient): 14/100 (14%, c.l. 8–22%); small bowel obstruction; 6/100 (6%, c.l. 2–13%).

We will consider the role of fraction size for these 4 types of complication.

Mediastinitis. Sixteen cases of post-radiation mediastinitis were observed out of 86 patients receiving 4 fractions of 2.5 Gy per week (19%). Thirty cases of mediastinitis were noted out of 54 patients treated with 3 fractions of 3.3 Gy per week (56%). The difference is highly significant ($p<0.001$). No adverse effect of additional chemotherapy to radiotherapy was found concerning the incidence of mediastinitis. In the '4×2.5 Gy' group, the incidence of mediastinitis was 13/69 (19%) when irradiation was given alone, and 3/17 (18%) when irradiation was combined with chemotherapy.

In the '3×3.3 Gy' group, the rate of mediastinitis was 19/35 (54%) for irradiation alone, and 11/19 (58%) for combined radiotherapy and chemotherapy.

It is worth noting that the chemotherapy schedules used in the 3 successive trials were either single agent vinblastine, a combination of vinblastine and procarbazine, or MOPP (mechloretamine, vincristine, procarbazine, prednisone). Neither regimen included radiosensitizing agents nor drugs directly toxic to the lungs. The absence of an adverse effect of chemotherapy on mediastinitis in this study cannot be extrapolated to other drug combinations, such as ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine).

Pericarditis. No case of pericarditis was observed in the 86 patients in the '4×2.5 Gy' group but 5 cases among the 54 patients in the '3×3.3 Gy' group (9%) were reported. The difference between the incidence rates of pericarditis is statistically significant ($p<0.01$). No adverse role of combined chemotherapy could be demonstrated.

Gastro-duodenal ulceration and severe gastritis. These complications were noted in 6 (10% out of 62 patients in the '4×2.5 Gy' group and in 8 (21%) out of 38 in the '3×3 Gy' group. Although there is a trend towards enhanced toxicity in the latter group, the difference is not statistically significant ($p=0.11$)

Chemotherapy appears to play an adverse role. In the '4×2.5 Gy' group receiving RT alone, the complication rate (ulceration and severe gastritis) was 4/57 (7%). When combined with chemotherapy, irradiation yielded a complication rate of 2/5 (40%). In the '3×3.3 Gy' group receiving RT alone, the complication rate was 4/26 (15%) and it was 4/12 (33%) for the chemotherapy-radiotherapy combination (test for trend: $p=0.033$).

Previous laparotomy clearly increased the risk of complications. In the '4×2.5 Gy' group, the complication rate (ulceration and severe gastritis) was 1/33 (3%) for no surgery-RT, and 5/29 (17%) for the surgery-RT combination. In the '3×3.3 Gy' group the complication rate was 2/21 (10%) for no surgery-RT, and 6/17 (35%) for the surgery-RT combination ($p=0.017$). This is in agreement with previously published studies at IGR (6, 10).

Small bowel obstruction. Three cases of small bowel obstruction were observed among the 62 patients in the '4×2.5 Gy' group (5%) and 3 cases among the 38 patients in the '3×3.3 Gy' group (8%). The difference is not significant ($p=0.41$). Neither combined chemotherapy nor previous laparotomy appeared to play an adverse role. The results are summarized in Table 2.

Complication fatalities. Four patients (4.5%) died from radiation injuries in the '4×2.5 Gy' group and 2 (3.5%) in the '3×3.3 Gy' group. The difference is not statistically significant.

In-field and marginal relapse. The number of fractions was analysed in relation to the risk of in-field and marginal relapses (associated or not to other type of relapse). We observed an adjusted risk coefficient of 1.39 (p=0.04) which suggests that a lower dose per fraction—the total dose being kept constant—is associated with a higher probability of 'local' relapse. By contrast, the rate of the other types of relapse, and the survival rate, were not significantly different in the '4×2.5 Gy' and '3×3.3 Gy' groups.

Discussion

Hodgkin's disease was treated at IGR until 1972 with ^{60}Co, to a total dose of 40 Gy with a schedule of 4×2.5 Gy per week. In 1972, the treatment was transferred to a 25 MV linear accelerator. For operational reasons due to machine time availability, the number of weekly fractions was reduced to 3. Based on a previous study on human skin desquamation (4) which had demonstrated no significant change of the total isoeffect dose when the dose per fraction was less than 3 Gy, it was decided to keep the same weekly dose of 10 Gy (3×3.3 Gy) for the reduced fractionation. In fact for most treatments carried out with this schedule at various sites (tonsil, oesophagus, lung, bladder), no difference was observed in tumour response nor normal tissue reactions with respect to the former experience of 4×2.5 Gy per week schedule on the Cobalt unit. In 1976 Le Bourgeois & Bouhnik (9) analysing the data of 69 patients with a follow-up between 6 months and 3 years observed an unusually high rate of complications. This could not be related to the irradiated volume nor to dose distribution. The fractionation regimen was suspected of being responsible for the detrimental effect. It was then decided to revert to 4 fractions of 2.5 Gy per week. The present paper reports the rate of late complications observed with the 2 schedules. It shows that the rate of complications which could be analysed was definitely higher after the 3×3.3 Gy weekly dose than after 4×2.5 Gy, with the same total dose of 40 Gy.

The first conclusion is that the lack of fractionation effect between 3 and 2 Gy fractions demonstrated for skin desquamation cannot be confirmed for late complications after treatment for Hodgkin's disease. For other tumour types treated with 3×3.3 Gy per week it has not been possible to reach definite conclusions. Most of these treatments were given for tumours (oesophagus, lung, bladder) with a poor prognosis, and the number of patients surviving at 2 years was too small for analysis. For squamous cell carcinoma of the tonsil, which has a better prognosis, no striking incidence of late complications was observed after treatment with the larger fractions but the treated volume was relatively small and the external beam treatment only contributed with 45 Gy to the whole treatment which also included an interstitial iridium-192 application. However, since 1976, an increase in the late complication rate had been suspected in patients irradiated for cancer of uterine cervix with large fractions and this has later on been confirmed (1).

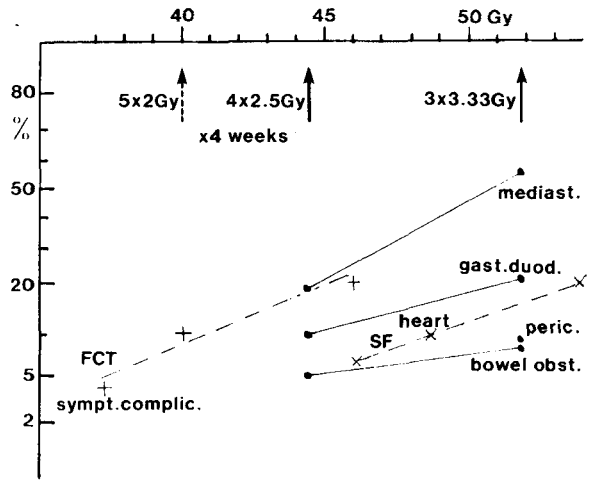


Figure. Complication rate of radiation treatment of Hodgkin's disease as function of the equivalent total dose with 2 Gy fractions. The actually given total doses have been converted into equivalent total doses delivered with 2 Gy fractions by using the α/β formula (α/β = 2.5 Gy). Blacks dots: present data. Dotted line FCT: data from Fazekas et al. (5). Dotted line SF: data from Stewart & Fajardo (13).

Table 3

α/β	10	5	2.5
Dose equivalent to 12×3.3 Gy=40 Gy when delivered by fractions of 2.5 Gy (in Gy)	42.6	44.4	46.6

Using the NSD formula, the dose of 40 Gy delivered in 12 fractions is equivalent to a dose of 42.8 Gy delivered in 16 fractions over the same overall time. Such a slight difference in the equivalent dose could hardly explain the important increase of complications between 16×2.5 Gy and 12×3.3 Gy.

According to the formula derived from the linear quadratic expression of the cell survival curve, a dose D delivered by fractions of d Gy is equivalent to a dose D' delivered by fractions of d' Gy if

$$D' = D\frac{\alpha/\beta+d}{\alpha/\beta+d'}$$

The results of the computation for various values of the α/β parameter are given in Table 3. A small value of α/β appears necessary to account for the large difference in complication rate. A value α/β=2.5 Gy has been tentative-

Table 4

Dose	Complication rate %	Equivalent doses with 2 Gy fraction α/β = 2.5 Gy Gy
A) Symptomatic complications (pneumonitis, myelitis, pericarditis) Fazekas et al. (5)		
20×1.9 Gy = 38 Gy	4	37.2
20×2 Gy =40 Gy	10	40
20×2.2 Gy = 44 Gy (29 days)	20	46.0
B) Carditis—Stewart & Fajardo (13) Dose presumably delivered by 2.2 Gy fraction		
42 Gy	0	43.9
44 Gy	6.6	46.0
46.5 Gy	10	48.6
51.5* Gy	20	53.8

* Retreatment

ly adopted for comparison of the treatment schedules considered in the present study with the more conventional regimen using a dose of 2 Gy per fraction.

Complication rates are plotted in the figure as a function of the equivalent total dose delivered with 2 Gy fractions. This graph also shows the rate of 'symptomatic complications' observed by FAZEKAS et al. (5) and the incidence of carditis observed by STEWART & FAJARDO (13). The data of these studies are given in Table 4; the equivalent dose with 2 Gy fraction has been computed for each schedules used assuming α/β=2.5 Gy. There is a fairly good agreement between the regression lines for mediastinal complication in our study and 'symptomatic complications' —presumably mainly pneumonitis—in the study of FAZEKAS et al. (5). The rate of heart complication reported in our study (pericarditis) is also in reasonable agreement with the findings reported by STEWART & FAJARDO (13).

In conclusion the rate of mediastinal and pulmonary complications can be assessed at approximately 10% for a dose of 40 Gy delivered in 2 Gy fractions (8) and that it is doubled by each additional dose of 4 Gy, in the range of doses studied.

With other fraction sizes, the total equivalent dose can reasonably be related to irradiation with 2 Gy fraction by using the α/β formula with a α/β value of 2.5 Gy. This value seems acceptable for the other less frequent late complication observed after treatment of Hodgkin's disease. The lower rate of local relapses in the 3×3.3 Gy group would suggest a relatively 'low' value of the α/β ratio (<10 Gy?) for control of Hodgkin's disease. However, the difference had borderline significance and the survival rate was not significantly different between the 2 fractionation groups, probably due to the efficacy of salvage treatments. The 3×3.3 Gy per week schedule could be—slightly—more efficient for local control (probably without influence on long-term survival rate); however, this possible benefit cannot balance the considerable increase of late complications.

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