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The Concept of the GPOH-HD 2003 Therapy Study for Pediatric Hodgkin's Disease: Evolution in the Tradition of the DAL/GPOH Studies

Konzept der Therapieoptimierungsstudie GPOH-HD 2003 für die Behandlung von Kindern und Jugendlichen mit einem Morbus Hodgkin: Evolution aus der Tradition der DAL/GPOH-Studien

Abstract

Today it is possible to cure more than 90% of children and adolescents with Hodgkin's disease with a combination of radiotherapy and chemotherapy. Since the DAL-HD 82 study, the main scientific focus has been on avoiding late effects such as the OPSI syndrome, late complications involving the heart, lungs, thyroid and/or gonads particularly sterility in men and premature onset of menopause in women, and the prevention of secondary malignancies. The GPOH-HD 2003 study will introduce FDG-PET to the initial diagnostic program and the assessment of response to therapy in order to evaluate further possibilities for reducing therapy. In this context, the central review of all clinical and radiological findings, systematically done since the DAL-HD 90 study, will be increasingly relevant in maintaining standardised stage classification and therapy group assignment which was established by the preceding studies. Continuing in the direction of

Zusammenfassung

Durch die kombinierte Radio-Chemotherapie können über 90% aller Kinder und Jugendlichen mit einem Morbus Hodgkin geheilt werden. Seit der DAL-HD-82-Studie steht die Vermeidung von Langzeittherapiefolgen – u. a. OPSI-Syndrom, Spätschäden am Herzen, der Lunge, der Schilddrüse und den Gonaden, und hier insbesondere die Unfruchtbarkeit beim Mann/vorzeitige Menopause bei der Frau sowie die Vermeidung von Sekundär malignomen – im Blickpunkt des wissenschaftlichen Interesses. In der GPOH-HD-2003-Studie wird die FDG-PET in das initiale Diagnostikprogramm und in die Beurteilung des Therapieansprechens eingeführt, um weitere Möglichkeiten zur Therapiereduktion zu evaluieren. In diesem Zusammenhang wird die seit der DAL-HD-90-Studie systematisch eingeführte Referenzbegutachtung aller klinischen und radiologischen Untersuchungsbefunde weiter an Bedeutung gewinnen, um die in den bisherigen

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the earlier studies, the indications for radiotherapy will be restricted even further. In the early stages (treatment group 1) patients with CR or a negative FDG-PET at the end of chemotherapy will receive no radiotherapy in order to reduce the risk of a secondary malignancy. In a randomized comparison, procarbazine will be replaced by dacarbazine in the COPP cycles to determine whether sterility in men and premature onset of menopause in women can be avoided by elimination of procarbazine while retaining the same clinical efficacy. Finally, relapse therapy is to be tailored according to the time of relapse, the initial therapy group, and the patient's response to the relapse therapy with more patients receiving autologous transplantation in order to further improve the results of relapse treatment.

Key words

Hodgkin's disease · children · GPOH · FDG-PET radiotherapy · dacarbazine

Studien erreichte Vereinheitlichung der Stadieneinteilung und der Therapiegruppenzuordnung zu erhalten. Der Tradition der Studiengruppe folgend soll die Indikation zur Radiotherapie weiter eingeschränkt werden. In der Therapiegruppe 1, d. h. den frühen Stadien, erhalten die Patienten mit CR oder einer negativen FDG-PET am Ende der Chemotherapie keine Radiotherapie. Hierdurch soll das Risiko für die Entstehung von Sekundär malignomen gesenkt werden. In den COPP-Zyklen wird Procarbazin im randomisierten Vergleich durch Dacarbazin ersetzt. Hierdurch soll geprüft werden, ob bei gleicher onkologischer Wirksamkeit die Unfruchtbarkeit beim Mann bzw. die vorzeitige Menopause bei der Frau durch den Verzicht auf Procarbazin vermieden werden kann. Auf der Basis der bisherigen Rezidivbehandlungen soll schließlich die Rezidivtherapie nach Zeitpunkt des Rezidives, initialer Therapiegruppe und Ansprechen auf die Rezidivtherapie gesteuert werden.

Schlüsselwörter

Morbus Hodgkin · Kinder · GPOH · FDG-PET · Dakarbazin

Introduction

Beginning in 1978, children and adolescents with Hodgkin's disease in Germany and Austria have received treatment in consecutive multicentre studies designed for therapy optimisation. Employing a combination of risk-adjusted chemotherapy and radiotherapy for all stages of disease right from the start, those studies have consistently produced cure rates above 90%, from the second study on above 95%. Thus, already from 1982 on (DAL-HD 82), the main focus of the study was a reduction of late effects. The DAL-HD 90 study introduced centralised review of the initial staging and therapy response as well as determination of the radiotherapy by a central review board. Likewise, the strategies for relapse treatment were developed in the context of the HD-ST (Hodgkin disease salvage therapy) 86 study. The strategies for the soon to be implemented GPOH-HD 2003 study is described below. The six predecessor studies were organised by Deutsche Arbeitsgemeinschaft für Leukämieforschung und -behandlung im Kindesalter from 1978 to 1995 (DAL-HD 78, HD 82, HD 85, HD 87, HD 90), and from 1995 on (GPOH-HD 95) by Gesellschaft für Pädiatrische Onkologie und Hämatologie. Based on the results and the technical advances made so far, the new GPOH-HD 2003 study has the following main goals:

- Evaluating FDG-PET in the context of initial staging diagnosis and for assessing the therapy response;
- Further reducing the risk potential for secondary malignancies by restricting radiotherapy;
- Further reducing the risk potential for causing injury to the male or female gonads by modifying the chemotherapy;
- As the reduction of treatment in newly diagnosed patients bears the risk of increased relapse rate suggestions will be given to further optimise the relapse treatment.

Introducing FDG-PET to the routine diagnostic programme in Hodgkin's disease: Centralised review of all clinical and diagnostic findings

Whole-body FDG-PET scans the entire body in a single investigation, thus making it possible to detect tumours anywhere in the body, whereas primarily localised methods like CT and MRI can miss lesions at unusual sites. Various studies have shown that more lesions are usually detected with FDG-PET than with CT/MRI [1–3]. Furthermore, histological review in selected cases with discordant diagnoses showed a sensitivity of 96% for PET vs. 4% for CT/MRI and a specificity of 79% for PET vs. 21% for CT/MRI [4]. For some patients, this would mean a different stage classification and intensity of therapy. In the GPOH-HD 2003 study, initial FDG-PET findings are to be used for determining the affected regions only where CT/MRI is inconclusive. An isolated focus of increased activity on FDG-PET in one region without a morphological correlate on CT/MRI does not justify a change in stage classification. Thus it will be seen whether or not patients are at a higher risk of relapse if a discrepant FDG-PET finding is ignored which would otherwise have necessitated a change in the intensity of therapy.

The DAL-HD 90 study was the first one to introduce centralised review of clinical data, MRI and CT scans for all children and adolescents with Hodgkin's disease. This means that the stage classification and the therapy group assignment of all patients was done centrally by a reference panel including experts in the fields of pediatric oncology, radiotherapy, radiology and nuclear medicine after evaluating the CT/MRI images together with the clinical data and the ultrasound findings. Evaluation of the DAL-HD 90 study showed that the stage had to be revised in about 20% of the patients following centralised evaluation. In respect to staging 11.7% of the patients were assigned to a higher therapy group while 1.6% were assigned to a lower group [5]. With FDG-PET being introduced to diagnostics within this study, centralised reference evaluation will be indispensable to ensure uni-

form evaluation of FDG-PET findings for deciding the course of therapy and for uniform staging and response assessment of all study patients.

At the weekly tumour conference at the study center, first the radiological findings are presented, followed by the PET findings. Since the CT/MRI findings and the PET evaluation are done independently by the reference radiologists and the nuclear medicine physicians, CT/MRI and FDG-PET can be evaluated prospectively in determining the regions affected by Hodgkin's disease. Finally, a definitive diagnosis will be made while also taking into account any ultrasound findings and clinical symptoms. Thereby the reference stage will be determined and subsequently used for assigning patients to the therapy groups.

FDG-PET for response assessment in adult patients with Hodgkin's disease

For mainly adult patients, the sensitivity of PET is variously reported as 50–100%, specificity as 64–100%. A recent meta-analysis of data from 278 patients with Hodgkin's disease revealed an overall sensitivity of 83.1% [6–12] and an overall specificity of 91.5% [13]. Due to the low prevalence of relapses, and despite the relatively low sensitivity, this yields a negative predictive value of >90%. However, relapses that occurred in this cohort of patients despite unremarkable PET findings after therapy were exclusively in patients with advanced stages.

Reducing the risk of radiotherapy-induced secondary malignancy

Longitudinal studies have shown that the occurrence of secondary solid tumours (SST) following treatment of Hodgkin's disease is a serious problem. The American Late Effects Study Group (LESG), which followed up on the post-HD incidence of secondary malignancy in 1380 paediatric patients over several decades, showed that the SST rate rises sharply 20–30 years after the primary therapy. The cumulative incidence up to 30 years follow-up was about 25% [14], although only a small number of patients could be followed over this long period of time. The most important risk factor for developing SST seems to be radiotherapy [15].

While the DAL-HD 78 study still applied extended-field irradiation with doses of 36–40 Gy [8], the later studies stepwise reduced the radiotherapy dosage. Thus, the patients in the GPOH-HD 95 study received only 20–25 Gy [16, 17]. The event-free survival (EFS) for all patients in the GPOH-HD 95 study was 88% after 5 years. This differs only slightly from the DAL-HD 82 study (96% EFS after 3.5 years with more intensive treatment which did have far fewer patients; [18]). Furthermore, in the GPOH-HD 2002 pilot study, the indication for increased radiation doses in regions responding poorly to chemotherapy has been reduced further. Thus, patients with a residual tumour volume of 50–100 ml in a given region receive only 20 Gy instead of the hitherto usual 30 Gy. An additional goal of the GPOH-HD 2003 study is to introduce 3-D-treatment planning to improve dose homogeneity at the tumour site.

Indications for radiotherapy have been changed or modified in the GPOH-HD 95 study for the first time. Patients with a complete remission (CR) at the end of chemotherapy received no radiotherapy. 5 year event-free survival for all patients was 88%, overall survival (OS) 97% [16]. EFS of irradiated patients was 92%, which was significantly higher than that of non-irradiated patients (88% EFS after 5 years). There were, however, differences between the different treatment groups. EFS after 5 years for TG-1 patients was 97% (without radiotherapy) or 94% (with radiotherapy), whereas TG-2 and TG-3 patients showed significantly worse EFS (TG-2: without radiotherapy 78% vs 92% with radiotherapy and TG-2 and TG-3: 79% without radiotherapy vs 91% with radiotherapy).

Nachman et al. [19] reported that the indications for radiotherapy for patients with early stages could be further reduced using Ga (gallium) scintigraphy. This study comprised 829 Hodgkin patients. Patients who showed a good partial remission (tumour volume reduction >70%) and a negative Ga scintigraphy at the end of chemotherapy were randomized for treatment with and without radiotherapy. In patients with early stages, a continuous remission rate of 89% was achieved without radiotherapy and 100% with radiotherapy.

The GPOH-HD 2003 study will continue on the course of therapy reduction. Thus, for patients in TG-1 indications for radiotherapy will be restricted further. Patients with a negative FDG-PET at the end of chemotherapy will receive no radiotherapy. FDG-PET will be used since many studies on adult Hodgkin patients showed that this method is well suited for detection of vital tumour in Hodgkin's disease and may be better than Ga scintigraphy, especially for assessing extramediastinal involvement [13].

The results regarding the positive and negative predictive value of FDG-PET follow-up studies for the prediction of disease-free survival are mainly obtained from adult HD patients in follow-up examinations. Recently, Dörffel et al. reported a negative predictive value of 94% and a positive predictive value of 25% for children and adolescents with Morbus Hodgkin treated in the GPOH-HD 95 trial [20]. Based on these results in adults and children, we expect a cure rate of 95% in patients with early stages without radiotherapy, when they are showing negative FDG-PET findings at the end of chemotherapy. While less favourable results cannot be excluded, there is a 95% Bayes' probability of the cure rate being >90% if the data available on the sensitivity and specificity of FDG-PET in Hodgkin's disease (60–80% resp. 75–95%) are correct (Hasenclever, in preparation).

Experience from the GPOH-HD 2002 pilot study on initial staging in children and adolescents with Hodgkin's disease reveals an important limitation for this strategy. Some of the patients present with lesions which, although negative on the initial FDG-PET, are diagnosed as affected when conventional methods are used. An interim analysis of the FDG-PET examinations done at initial staging so far (as of October 2003) has shown 36/1095 discordant negative lymph node sites (3.3%) and 2/196 extralymphatic localisations (1%). The 38 discordant negative results were obtained in 24 of the 53 patients included in the analysis. However, in TG-1 only in 6/19 patients discordant negative PET findings were seen. In the case of such a discordant negative PET finding,

the local response in that region cannot be assessed using FDG-PET. Nevertheless, in the GPOH-HD 2003 protocol patients with a discordant negative FDG-PET finding in the initial staging will receive no radiotherapy if they have a completely negative FDG-PET at the end of chemotherapy and the regions with initially discordant negative PET findings are in complete local remission, i. e. the lymph node masses in this region are <5% of the initial volume and <2 ml residual volume.

Regarding the time point, when a FDG-PET scan should be performed after a chemotherapy, the EORTC recommends that no PET scan should be done 1–2 weeks after chemotherapy, since in addition to false-positive results, higher rates of false negative results have been observed in patients with malignant germ cell tumors [21].

For the advanced stages (TG-2 and TG-3) it has so far not been possible to identify patients with a very good prognosis and those expecting to do very poorly at the time of initial diagnosis.

The GPOH-HD 95 study has shown that the “no radiotherapy” strategy for TG-2 and TG-3 patients with complete remission at the end of chemotherapy is associated with a higher relapse risk [16]. In the preliminary studies, no specific prognostic factors have been evaluated to identify patients with good or poor prognosis in these treatment groups. Therefore, in the GPOH-HD 2003 study all patients in TG2 and TG3 will be irradiated at the end of chemotherapy. In the GPOH-HD 95 study B symptoms, nodular sclerosing type 2 histology, extranodal involvement and stage IV were found to be independent risk factors [22]. For patients with two or more risk factors, EFS is 80% and 73% for patients with or without radiotherapy. Despite the inferior treatment results in patients with two or more risk factors, we see no justification to intensify therapy since at the most 27% of patients would profit whereas 73% would receive a needlessly intensive therapy.

Using Ga scintigraphy, it could be shown that early response to therapy is associated with a better prognosis. Of 24 Hodgkin's disease patients with negative Ga scintigraphy after one completed course of chemotherapy, 92% remained in complete remission. Of 78 patients with a negative Ga scintigraphy halfway through the course of chemotherapy, 82% remained in complete remission. On the other hand, 4/7 patients who still had a positive scintigraphy after chemotherapy relapsed [23].

The studies on the value of FDG-PET for estimating prognosis show a highly significant correlation between positive PET findings and decreased EFS of Hodgkin's disease patients [11, 24]). Moreover, Kostakoğlu et al. [25]) showed that positive PET findings after one cycle of chemotherapy are associated with a significantly lower progression-free survival. Taken together, these results indicate that an early response to chemotherapy is associated with a better prognosis. Hence, the GPOH-HD 2003 study is to ascertain whether TG-2 and TG-3 patients with negative PET findings after 2 chemotherapy cycles have a favourable prognosis which might allow reduction of radiotherapy. Furthermore, it will be examined whether patients with a positive PET after 2, 4, or 6 chemotherapy cycles have such a poor prognosis that it would justify intensifying the therapy at an early time point.

Further reduction of chemotherapy-induced sterility in men or premature menopause in women

After the gonadotoxic effects of procarbazine within the OPPA and COPP cycles became apparent, procarbazine was eliminated completely from the DAL-HD 85 study. Thus, only three types of drugs were administered during the first two cycles and procarbazine was replaced by methotrexate for the COPP cycles [26]. This did prevent sterility in boys [27, 28], but also affected outcome. Patients with early stages had a 10-year-EFS of only 85%. 3-year-EFS was 59% for TG-2 patients and 62% for TG-3 patients. However, it was possible to save nearly all patients with salvage therapy though, and overall survival after 10 years was 98% [29].

For that reason, initial therapy in the DAL-HD 90 study was re-intensified. All girls received OPPA again. Boys received OEPA, i. e., procarbazine was replaced by etoposide in the hope of preserving fertility [30]. This strategy yielded 5-year-EFS rates of 91% (OPPA) and 89% (OEPA). Overall 5-year-survival in both groups was 98%. In boys with early stages, who received no procarbazine, but etoposide, the sterility rate was reduced to almost zero [31], while part of the TG-2 and TG-3 patients continued to show abnormal FSH values after the COPP cycles. According to the long-term follow-up analysis of the GPOH-HD study group the introduction of etoposide has not increased the rate of secondary leukemias [32].

Fertility in women seems to be less susceptible to chemotherapy, although there is a risk even for young women to show premature ovarian insufficiency and to enter menopause too soon. Longitudinal studies have shown that women who as teenagers had received radiotherapy below the diaphragm and/or chemotherapy with alkylating agents showed a clearly higher rate of premature menopause than did healthy controls [33]. This also seems to apply to women who received COPP as part of a therapy for Hodgkin's disease. Observing female patients who were younger or older than 24 years when they received COPP, Kreuzer et al. [34] found that 2/7 (<24 years) resp. 6/7 (>24 years) showed ovarian insufficiency and premature menopause following chemotherapy.

In order to prevent sterility in boys with advanced stages and premature menopause in females, the GPOH-HD 2003 study investigates a randomised comparison whether procarbazine can be replaced by dacarbazine in the COPP cycles (COPDIC cycles). Dacarbazine is effective against Hodgkin's disease and approved. Already in 1972, Frei et al. [35] tried dacarbazine as a single agent in previously treated patients with Hodgkin's disease, achieving 56% “objective remissions” at 5 daily doses of 250 mg/m² each over a period of 3 weeks. Klener and Donner [36] treated 10 HD patients who had become resistant to combination chemotherapy by administering 300 mg/m² DTIC i. v. on 5 consecutive days in 4 week intervals, achieving complete remission in 2 patients and partial remission in 7. Male patients do not usually show azoospermia after 6 ABVD cycles, either. The GPOH-HD 2002 pilot study is testing dacarbazine tolerance in the modified COPP cycles (COPDIC), with preliminary data indicating good tolerance. In 62 cycles, grade IV CTC toxicity was reported once each for neutropenia and for pain. No severe undesirable events were reported for the COPDIC cycle.

Therapy of children and adolescents with relapsed Hodgkin's disease

So far, data from the DAL-HD and GPOH-HD studies have shown that patients with a relapse following primary therapy for Hodgkin's disease have a realistic and, by international comparison, good chance for cure by a combination of chemotherapy and radiotherapy. The probabilities for EFS and overall survival (OS) after 4.5 years were 71% and 88% [37].

Both our own results and data from adult patients indicate that the time of onset of a relapse is of prognostic impact. Patients with a progression (i.e., therapy failure during ongoing therapy or within 3 months after the end of therapy) show a disease-free survival (DFS) of 42% and an overall survival (OS) of 50% after 10 years. The DFS rate for patients with an early relapse (<12 months after the end of therapy) is 53%, whereas DFS and OS for patients with a late relapse (\geq 12 months after the end of therapy) are 84% and 88% (Schellong in preparation).

Treating adult patients with a chemosensitive relapse of Hodgkin's disease, Schmitz et al. [38] showed that, freedom from treatment failure (FFTF) after 3 years was significantly better for patients with autologous stem cell transplantation (SCT) than for patients with conventional chemotherapy. This was especially true for patients with an early relapse (<12 months), but also for those with a late relapse. Patients with multiple relapses, on the other hand, do not profit from autologous SCT. Baker et al. [39] and Williams et al. [40] did a retrospective matched pairs analysis on data from paediatric and adult patients for the European Group for Blood and Marrow Transplantation (EBMT) and found no significant differences regarding progression-free survival. It seems that paediatric and adult patients with relapsing and refractory Hodgkin's disease respond similarly to high-dose chemotherapy with autologous SCT.

One of the most important parameters for the outcome of autologous and allogeneic SCT is the patient's status at the time of transplantation [41]. Becherer et al. [42] recently showed that patients with negative PET findings prior to high-dose therapy and autologous SCT have an excellent prognosis, whereas most of the patients with positive PET findings presented with a relapse. However, the number of cases examined is still too small for final conclusions.

The GPOH-HD 2003 study will be the first to conduct a relapse therapy where the time of onset of the relapse and the type of preceding therapy are systematically used as stratification characteristics. Based on the good results in adult patients with Hodgkin's disease [43], children and adolescents will also receive the combination DHAP (High dose cytarabine, dexamethasone and cisplatin) as part of the relapse therapy.

Since experience with adult Hodgkin patients has shown that the prognosis for patients with a relapse can be further improved by using high-dose chemotherapy followed by autologous stem cell transplantation [38], the indication for this type of therapy is to be extended to children and adolescents as well. However, in order to avoid needlessly high acute and long-term toxicity in relapse patients, the response to relapse therapy – including FDG-

PET – will be introduced as a further stratification characteristic. This is done to avoid unnecessary autologous transplantations, especially in patients with a late relapse (i.e., following primary therapy in TG-2 or TG-3).

Cost-benefit analysis for FDG-PET examinations

As part of the study protocol, all study patients will have at least two FDG-PET examinations. The participating institutions will be compensated for material expenses and personnel costs. On the average, this will be about 350.00 € per institution. While for TG-2 and TG-3 patients FDG-PET follow-up examinations will be conducted to determine a prognostic factor, there will be immediate therapeutic consequences for TG-1 patients since patients with a negative FDG-PET at the end of chemotherapy will receive no radiotherapy. The costs for one initial FDG-PET examination and another after chemotherapy will be 70 000.00 € for every 100 TG-1 patients. We hope that 80% of all patients in TG-1 can be spared radiotherapy without a drop in the cure rate. Planning and carrying out 3D-conformal irradiation for the typical TG-1 patient costs about 1100 € in Germany, i.e., 110 000 € for every 100 TG-1 patients. Thus, using the strategy of the GPOH-HD 2003 study, it will be possible to save about 88 000.00 €. An approximate amount of 22 000.00 € must be deducted from this, however, as using the strategy of the GPOH-HD 95 study already would have eliminated radiotherapy for about 20% of the TG-1 patients. Therefore introducing FDG-PET and elimination of radiotherapy in PET negative patients almost balances costs. Provided that the cure rate of the TG-1 patients with a negative FDG-PET after chemotherapy (judging from the experience made with FDG-PET so far) is as high without irradiation as it is with the currently used radiotherapy, and further assuming that if eliminating radiotherapy, the current 30-year-SST (secondary solid tumour) rate of about 20% of the patients with radiotherapy might be lowered to <5% of the patients without radiotherapy, there can be considerable expense reductions if diagnostics, operative and medical SST therapy, loss of man-hours, curative measures, pension payments, tax loss due to disability, etc. are all included in the calculations. In summary, there is reason to hope that introducing FDG-PET will be advantageous not only for the patient, but that it will also entail economic benefit. However, for patients in TG-2 and TG-3 cost benefit analyses have not been performed, because these analyses might not yet be important. Only if early or late response determined by FDG-PET truly proves to be a relevant prognostic factor, this concept might be introduced into the future routine diagnostic program (Table 1).

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Table 1 Differences between the GPOH-HD 2003 and the GPOH-HD 95 protocols

| GPOH-HD 95 | differences between the protocols | GPOH-HD 2003 |
|---|--|---|
| not applied | FDG-PET before and after two eventually also after four or six chemotherapy cycles in patients of TG-2 or TG-3 | standard |
| boys: OE(4)PA girls: OPPA | 1 st and 2 nd courses of chemotherapy | boys: OE(5)PA girls: OPPA |
| COPP | 3 rd to 6 th courses of chemotherapy | COPP vs. COPDIC |
| full remission after chemotherapy in TG-1, TG-2, TG-3 | indication for "no radiotherapy" strategy | full remission or negative PET after chemotherapy in TG-1 |
| 2D-field irradiation after the end of chemotherapy | radiotherapy planning TG-2 and TG-3: establishing the definitive radiotherapy dosage | CT-based 3D conformal after two courses of chemotherapy, i. e., before randomisation |
| 35 Gy | radiotherapy in residual tumour volumes 50–100 ml | 20 Gy |
| 35 Gy | maximum radiotherapy saturation up to | 30 Gy |
| mandatory | irradiation of the spleen in case of paraaortal lymph node involvement | done only in case of involvement of the spleen or the splenic hilum |
| time of relapse, initial therapy | stratification of relapse therapy | time of relapse, initial therapy and response to relapse therapy |

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