Staging Hodgkin's lymphoma: why and how?

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The initial work-up of Hodgkin's lymphoma involves a highly variable set of procedures. It depends on the type of treatment planned, the endpoint of the treatment strategy, the typical failure pattern, and on which treatment complications are expected. As it also depends on the level of knowledge and curiosity of the individual physician in charge, it differs from one center to the another even more than treatment guidelines do. The way staging procedures have evolved over the last 40 years shows how, although each technique has been replaced by a more sophisticated one, the same basic requirements remain. Indeed, even if one technique characteristic of a specific period has disappeared from routine use, each period has left intact a stratum of knowledge which is still valuable, or worth being rediscovered. Staging relates to the initial inventory of the presence of the disease, the reassessment of response at the end of treatment, or during treatment, the prognostic factors that can be used to select treatment, and the tools to measure (and to prevent?) short and long-term sequelae.

Initial disease inventory, laparotomy is still the best

The Sixties. How initial work-up is closely linked to a radiotherapy-based treatment is illustrated by the pioneering era of exploratory laparotomy, before this became a standard procedure, i.e. as the staging laparotomy. This story is worth telling in detail,[1] because the time for a meticulous and comprehensive inventory may have come back.

To analyze the characteristics of a man's life, Claude Bernard advised entering the living organisms using vivisection procedures: this advice was followed by S.A. Rosenberg, who required vivisection in the form of an exploratory laparotomy to resolve the case of a patient with an equivocal lymphangiogram preventing administration of appropriate portals of radiation therapy (RT); this was a full success for this patient who was still in his first remission ~25 years later. Why did we do such a heavy procedure? In the Sixties, prophylactic irradiation of uninvolved areas (based just recently on megavoltage therapy and extended field techniques) was thought to be of value only in supradiaphragmatic areas. It was intended to avoid recurrence developing in the immediate vicinity of a field too narrowly irradiated. Infradiaphragmatic and visceral involvement, known to occur from autopsy series, was thought to characterize end stage disease. Although lymphangiography turned out to be positive more frequently than expected, only the first exploratory laparotomies revealed how frequently para-aortic nodes and the spleen were involved, and responsible for treatment failures.[1,2] The range of lymphangiography limited to para-aortic and iliac nodes, and the frequency (~20%) of false positive and negative findings had prevented understanding of the natural history of the disease. Laparotomy was, therefore, essential to catch how the disease was spreading. Still, this early work of Kaplan and Rosenberg uncovering the intimate mechanism of Hodgkin's disease propagation was not pursued long enough. The reason is that the oncologist became too confident, assuming that extensive RT and/or adjuvant chemotherapy (CT) would literally erase any remaining microscopic disease. So why should the attempts of Hutchison and Tubiana to investigate a pattern of spread by contiguity, or those of Smithers about a random distribution of the disease make any difference?

The Seventies and the Ann Arbor staging procedure

Conventional laparotomy staging refers to radiation-based treatment. Laparotomy had some *a posteriori* impact on treatment by identifying and correcting erroneous evaluations of disease spread. But the reason why it was so popular was because physicians were persuaded that, in patients with localized disease, any relapse of Hodgkin's disease (considered at that time to be due to insufficient RT) would eventually be fatal. Laparotomy was considered the optimal safeguard to tailor abdominal irradiation in response to each individual patient's presentation. The Ann Arbor classification was based on the alleged benefit of laparotomy staging. Although symbols such as H +/-, N +/-, M +/- only pointed out the pathological stage (= biopsy of the organ), as compared to the clinical stage, the initial letter (S +/-), denoting the spleen, indicated that the information had been obtained through a laparotomy. The abbreviation PS for pathological stage, as intended initially and written, prevailed until the Eighties, standing ambiguously for post-surgical stage, as many thought it meant.

The last twenty years and the disappearance of the staging laparotomy

In a first step, laparotomy was deleted from the staging of localized disease (EORTC H5 Unfavorable patients trial) when sufficient clinical evidence suggested a need for either extended irradiation or adjuvant chemotherapy, for instance in patients with poor prognosis.[3] Later on, even in patients with the most favorable outlook (EORTC H6 Favorable patients trial), laparotomy staging

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and treatment adaptation proved not to be very rewarding in terms of tumor control and indeed to be worrisome in terms of immediate and late effects, as compared to clinical staging and subtotal nodal with splenic irradiation (STNI).[4] The next step toward renouncing staging laparotomy came from the superior results of combined involved field (IF) RT to the supradiaphragmatic areas only + adjuvant light chemotherapy over STNI.[5] Indeed, adjuvant CT was of benefit to all cases of localized disease (~75% of HD patients) and rendered accurate infradiaphragmatic staging of no interest.

At the beginning of the new Millennium

The situation now is exactly opposite of what has been true these last twenty years, for three good reasons: 1) RT is still needed. Indeed, most relapses occur in involved non-irradiated nodal areas after treatment with chemotherapy alone; even in good prognosis early-stage HD, the relatively light chemotherapy combinations that are used in short courses are unable to eliminate the microscopic disease left in-between the areas treated with IF RT. This was highlighted in the EORTC H9F trial in which the chemotherapy-alone arm had to be stopped because of an unacceptably high rate of relapses; 2) the involved -filed RT technique may be associated with delayed in-field elapse rate as high as 10%; 3) the RT fields need to be made smaller because of the high price paid in terms of toxicity in previous trials that used full dose extended fields.[4-7]

In conclusion, irradiation to the involved nodal areas (or less than nodal areas?), at least in stages I-II, should be continued. Therefore it is essential to know which areas are involved.

Initial inventory in the absence of laparotomy

Several steps can be taken to reduce the toxic burden of RT. These are:

(a) to taper the doses in non-involved areas of the extended field (EF) irradiation, according to the results of the German Hodgkin Study Group HD-1 study 20 Gy ≅ 40 Gy (GHSG HD-1 trial) and ≅ 30 Gy (non-randomized arm GHSG HD-5 trial);
(b) to prefer IF RT (EORTC choice since the H7 trial in 1988; tested in a randomized trial against EF RT in the HD-8 trial by the GHSG);
(c) to reduce doses even for IF RT (randomized EORTC H9F trial 20 Gy versus 36 Gy; H9U trial all 30 Gy); randomized HD-10 trial of the GHSG 20 Gy versus 30 Gy);
(d) to irradiate only the involved nodes, i.e. less than the involved area, as advocated by a few specialists. Intensity-modulated radiation therapy[8] may be the tool to achieve this task, provided that adequate safety is ensured by efficient quality-control programs.[9]

This is why better knowledge on the pattern of spread by contiguity, or on a random distribution, would now be so helpful. Nevertheless, only one study has been devoted to this subject.[10,11] Based on a series of laparotomy-staged patients, the study described the pathways of successive involvement of nodal areas according to the initial site involved by the disease, usually the right cervical area.

Unfortunately, although better knowledge of serial node involvement in HD would be very helpful, no additional series have been reported to confirm and expand the data produced by Roth.[17] And yet these data are needed because of the unacceptably high rate of cardiac complications and second tumors, which are responsible for extra early deaths in this population of young patients. To determine which nodes are involved, the only ones that ideally irradiation should encompass, and in the uncertainty about the likely path of this serial node invasion, the initial work-up should be reinforced.

Are newer diagnostic procedures validated? There have been attempts to correlate results from Gallium-67 scanning with those from a lymphangiogram. In 94 patients with localized Hodgkin's disease, including 51 patients who undergone a laparotomy, the sensitivity of computed tomodensitometry (50 to 25%) and lymphangiogram (42%) was higher than gallium-67 scanning at detecting nodal involvement (27%).[12] Unhappily, because of the disaffection with laparotomy, none of these new procedures, including immunoscintigraphy using radiolabeled anti-CD30 antibodies, could be studied extensively enough by comparison to lymphangiogram or to tomodensitometry.[13] The failure of newer techniques may be the reason why the place of laparotomy has been well preserved in the Cotswolds classification.[14] Conversely, fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) improved the diagnostic accuracy in the staging of HD, based on the metabolic signal of the lesions. For instance, FDG-PET detects supraclavicular, axillary and inguinal node involvement better. It is also sensitive at detecting visceral although this is questioned concerning bone marrow involvement.[15-17] Initial FDG-PET may not, however, yield more information about infradiaphragmatic nodal involvement than does CT-scan,[15] and certainly needs additional assessment. Nevertheless, it provides first order benefits when inserted in the initial staging. Indeed, its importance, in case of localized disease after conventional staging, comes from its ability (a) to detect additional nodal involvement worthy of irradiation (b) to rule out visceral involvement, since in case of stage IV disease both brief/light CT and irradiation would be detrimental to the patient.[18,19]

The ideal initial work-up should, therefore, include:

(a) a CT-scan of all nodal areas, particularly cervical and axillary nodes, as is now mandatory in the EORTC staging for patients with localized disease;
(b) FDG-PET scan to design the irradiation fields

before any treatment is started;
(c) image fusion integrating the PET scan.

These staging procedures would best allow the use of static and dynamic intensity-modulated radiation therapy and protect organs at risk.

Assessment of response to initial treatment

Cheson's criteria for the assessment of response at the end of treatment are based on CT-scanning. This crucial assessment usually relies on a comparison with the studies performed at initial work-up, although its results could stand by themselves. If the type of response directs the rest of the treatment (as in most current HD trials), then response criteria are of primary importance.[20] The EORTC advocates the use of Cheson's criteria. Although they were designed for non-Hodgkin's lymphoma, they also make a lot of sense for HD.[21] The main features are:

(a) after treatment a normal lymph node must not exceed 1.5 cm in maximum diameter on CT-scan;
(b) in previously involved nodes a complete response (CR) is defined as a decrease by more than 75% in the sum of the products of the greatest diameters (SPD);
(c) a complete response/unconfirmed (CRu) in patients is a residual mass but greater than 75% reduction in tumor size after therapy representing a non-active disease mass;
(d) use of CT scans as standard procedure for evaluation of nodal disease: *thoracic, abdominal, and pelvic CT scans are recommended even if those areas were not initially involved because of the unpredictable pattern of recurrence in NHL*;
(e) introduction of the concept of *modulated response assessment*, which means assessment at intervals depending on the type of treatment: *studies should be performed no later than 2 months after treatment has been completed to assess response. This interval may vary with the type of treatment: a longer period may be more appropriate for biologic agents where the anticipated time to response may be greater*;
(f) selection of event-free survival (time to treatment failure), which includes failure or death from any cause as the optimal end-point;
(g) concept of the utility of treatment reflected in response assessment: *for patients with an indolent NHL, response duration may be less clinically important than the point at which initiation of treatment is necessary*.

Cheson's criteria are based on two-dimensional measurements of one or several target lesions.[21] They are in line with the recommendations made by the WHO in 1979 for reporting treatment results.[22] These criteria have been challenged by the RECIST (*Response Evaluation Criteria In Solid Tumor*), based on one-dimensional measurements. RECIST demonstrated less bias, was simpler and quicker for the radiologist, but it has only been validated for solid tumors.[23] A recent study assessed the RECIST for HD.[24]

Gallium scanning (^{67}Ga) is part of Cheson's recommendations. It is best used in the presence of a residual mass on conventional imaging (CT-scan) to distinguish HD from non-specific changes and to correlate residual disease imaged with ^{67}Ga uptake and *eventual likelihood of recurrence*.[21] Single-photon emission computed tomography (SPECT) with gallium scanning demonstrated a higher sensitivity, specificity, and positive and negative predictive values. Nevertheless, predictability of cure (sensitivity) in the mediastinum, is not excellent.[25] A representative example in 62 lymphoma patients (n=52 HD) where ^{67}Ga scintigraphy was also performed after therapy (n=42) using 185-220 MBq ^{67}Ga citrate and planar and SPECT studies. In this study, a residual mass was observed in 31/42 CT scans and ^{67}Ga imaging was normal in 22 of these 31 cases (71%); only 4 of the 22 patients relapsed (8-45 months interval). Predictability of relapse (specificity) was excellent, since 8/9 patients with abnormal ^{67}Ga uptake in a large residual mass relapsed within 30 months.[26] Other studies confirmed that gallium scanning is helpful to avoid unnecessary complementary treatment or in directing a change of treatment modalities.[27,28]

Several studies compared CT-scan and FDG-PET for the diagnosis of residual masses.

(a) In 37 HD patients both CT-scan and FDG-PET were performed after treatment.[29] Sensitivity and specificity (detection of relapses) were much better for FDG-PET (91% and 69%, respectively) than for the CT-scan (72% and 21%, respectively). Furthermore, only the result of FDG-PET was positively correlated with event-free survival.
(b) Of 54 patients (HD and NHL) showed a residual masses on CT; 18F-FDG PET was positive in 5 of those 24 patients with residual CT mass and in only 1 of 30 patients without. All 6 patients (100%) with positive FDG PET relapsed, whereas 5/19 patients (26%) with residual masses on CT but negative FDG PET, and 3/29 patients (10%) with negative CT scan and ^{18}F-FDG PET studies did so. The positive predictive value was much higher for the FDG-PET: 100% v 42%. Furthermore, a positive FDG PET was also associated with poorer 1-year survival than was a negative study: $50\pm20\%$ versus $92\pm4\%$ ($p < .0001$).[30]

The same property explains the probable superiority of FDG-PET over gallium scanning in the diagnosis of residual masses.[31]

Medicare in the USA recognized expansion of coverage (effective July 1, 2001) for usage of PET for the initial staging, and restaging of both Hodgkin's and non-Hodgkin's disease. More specifically the clinical situations covered are when *(i) the stage of the cancer remains in doubt after completion of a standard diagnostic work-up, including convention-*

al imaging (computed tomography, magnetic resonance imaging, or ultrasound) or, (ii) the use of PET would also be considered reasonable and necessary if it could potentially replace one or more conventional imaging studies when it is expected that conventional study information is insufficient for the clinical management of the patient and, (iii) clinical management of the patient would differ depending on the stage of the cancer identified. PET will be covered for restaging after the completion of treatment for the purpose of detecting residual disease, for detecting suspected recurrence, or to determine the extent of a known recurrence.."[32]

Additionally FDG-PET can be coupled with CT-scan (radiological image fusion) a promising technique to design irradiation strategies.

Assessment of prognostic factors

Consensus on prognostic factors still differs according to the apparent extent of the disease, localized or advanced presentation. One should note that in both circumstances the same characteristics tend to be retrieved, especially when analyses are adjusted for treatment.[32]

Localized disease presentation

(a) in the early seventies, very quickly after it was first reported, the EORTC challenged the therapeutic value of laparotomy. The H2 trial proved that, in the absence of treatment adaptation, event-free survival and survival were similar in patients randomized to clinical staging and STNI + spleen irradiation instead of laparotomy + splenectomy.[34] Conversely, staging laparotomy and splenectomy brought prognostic information which has been in use for 20 years: spleen involvement predicted further nodal relapse (13% relapses in non-irradiated areas, a 17-fold increase) and extranodal relapses (16%, a 2-fold increase),[34] but this prognostic information was apparent only in the best prognostic group, and exclusively on freedom from progression.

(b) many teams attempted to stratify HD treatment according to a specific set of initial characteristics, beyond the Ann Arbor and Cotswolds staging classifications. For example, the EORTC proposed, on the basis of analysis of 1392 patients,35 a simple stratification into 2 main groups (favorable and unfavorable), calling for registration of tumor-related factors (number of initial clinically involved areas, a combination of systemic symptoms and accelerated erythrocyte sedimentation rate, bulky mediastinum) and of patient-related factors (age < or ≥ 50 years, sex), that has been widely adopted in Europe (EORTC, GHSG, GELA) and in the USA.

Advanced disease presentation

The recent international prognostic score (IPS)[36] lists 7 unfavorable factors: albumin < 4 g/L ; Hb < 10.5 g/L ; sex (male); stage IV ; age ≥ 45 years; WBC > = 15×10^9/L; lymphopenia < 0.6×10^9/L or < 8%; these factors are correlated with the event-free survival. Treatment stratification may be performed according to the number of factors present.

There can be pitfalls in all staging systems. These may concern:

(i) statistical methods on judgement criteria that rely on the time elapsed;

(ii) techniques for assessing the patient's and disease characteristics, initial work-up, response and treatment parameters;[33]

(iii) the prognostic models in which it is not known whether missing characteristics are due to lack of data or lack of significance; consensual characteristics are not being tested in multivariate analyses when new, odd and strange characteristics are put forward;

(iv) standardization limitations: for instance there are many different ways to measure the bulk of a mediastinal mass, the nodal areas involved, the B symptoms, the marrow involvement, the biological markers (Cu^{++}, albumin, LDH). Standardization through fractions/multiples of normal or broad standard errors make differences; assessment of response (according to the type of work-up [CT-scan ± ^{67}Gallium or FDG-PET]), the time elapsed from last treatment or last CT. Irradiation allows more time for mass resolution and increase, *ipso facto*, the CR rating. The Cotswolds classification induces more variation both through the concept of CRu and by allowing some flexibility in the time range in which the response needs to be recorded.[14]

In all stages, prognostic factor classifications are relatively easy to correlate to the progression/relapse, at difference to the survival endpoint. Apart from the difference in the number of events, this is probably because of a stronger interaction with the patient's characteristics (age, immunosuppression, intercurrent diseases) and ability to deliver the more intense treatments properly. However, 3 sets of data may be of value to identify prognostic factors which influence response/relapse criteria on one hand and survival on the other. 1) *Tumor mass.* Bulky mediastinum is probably less reliable than the tumor burden, valid for both localized and advanced HD, and for supra- as well as infra-diaphragmatic presentations.[37] The most convincing results have been obtained when the volume of all disease sites have been taken into account in proportion to the body.[38] 2) *Biological characteristics.* It is tempting to investigate whether the particular environment Reed-Sternberg cells, these cells' extraordinary mechanisms of apoptosis resistance (NF-kB activation), and their system for immune escape (CD30L, CD40L, LMP1, TNF) can be correlated to the prognosis in the individual patient. A recent paper confirmed the value of sCD30 determination.[39] A prospective effort is being made to correlate some of these factors, in a reproducible and quantitative way, to standard prog-

nostic end-points, and promising results have been observed with the combination of CD30s, IL1RA, IL6, as compared to the IPS. For this purpose systematic serum and tissue banking are needed, as currently performed by the GHSG and the GELA. 3) *Mid-treatment response*. This is a powerful surrogate to predict outcome.[40] Two hundred and seven patients with stage IIIB-IV Hodgkin's disease underwent an EORTC study *to assess, prospectively, the interval to reach an apparent complete response, and its meaning, through repeated tumor measurements every 2 cycles. Patients who were assessed, on clinical, biological and imaging criteria, as complete responders before cycle #5 (CR4 patients), as compared to the other responders had a higher 15-year freedom from progression (FFP) (61% versus 37%, p< 0.001) but also survival (61% versus 41%, p= 0.001). This observation is not due to patient-related confounding factors since the survival advantage in CR4 patients all comes from the avoidance of HD progression-related deaths (HD-specific survival = 85% in CR4 patients versus 60%, p< 0.001) and does not concern the other deaths (non HD-specific survival 74% versus 71%, p = 74).* Assessment of early response can be used in CR4 patients to decrease the number of cycles to be given, or to avoid overtreatment; in poor responders it may help to switch early enough to another treatment. These surrogates have been applied successfully to the strategies developed in the subsequent 20884 advanced HD EORTC trial.18 In NHL, early FDG-PET (after 2 - 3 cycles of chemotherapy), when positive, proved predictive of failure (4/5) or relapse (5/5), demonstrating a very high specificity.[18,41] Another study, in 30 patients with NHL or HD, confirmed this observation and suggested that very early FDG-PET assessment had greater sensitivity (less false negative) when performed during initial CT than after CT ended.18,42 However, use of PET to monitor tumor response during the planned course of therapy (i.e. when no change in therapy is being contemplated) is not covered in the USA by Medicare: "*restaging only occurs after a course of treatment is completed, and this is covered...*".[18,32]

Assessment of treatment compliance and long-term sequelae

Assessment of treatment compliance, long-term sequelae,[6,7,18] and quality of life (QoL),[18,43] needs to be inserted in the initial work-up. For instance the EORTC has been prospectively monitoring pulmonary, cardiac and gonadal function since the H6 trial, started in 1982. Apart from standard assessment of the patient's history (biological work-up, HIV & hepatitis serology, etc.), the following tests have been performed repeatedly: thyroid function (T4, TSH); fertility tests (FSH, LH, estradiol, progesterone, testosterone, spermogram, andrological examination and sperm preservation); cardiac function (isotopic or ejection fraction at rest); pulmonary function (vital capacity, forced expiratory volume, functional residual capacity, CO diffusion capacity). If these studies may be of benefit to an individual patient, one must recognize that their yield concerning quantification of specific treatment toxicity,[44] and global treatment strategy remains dismal. The absence of standardized tests may account, in part, for the relatively poor compliance with test performance and unwillingness to retrieve the data. Monitoring quality of life, through longitudinal questionnaires, has been more successful.[45]

Second tumors[6] are increasingly being taken into account in the design of treatment strategies. However, co-factors are rarely recorded. Only the last Hodgkin Intergroup trial (#20012) records patints' smoking status and familial cancers. Although few prospective cohort studies are available, screening for cancer (breast) may be rewarding.[46]

Conclusions

The reason why the initial work-up for Hodgkin's lymphoma includes a set of procedures of primary importance is that these allow optimal control of the type of treatment planned, the endpoint in the treatment strategy, check on the failure pattern typical of the presentation, as well as evaluation and prevention of expected treatment complications. because it needs to be adapted, no *standard* work-up is proposed, neither exists. It must address, however, accurate initial extent of the disease, disease-related prognostic factors, and — in relation to the treatment planed — check-up of patient medical condition, anticipation of QoL burden and late toxicities.

Current techniques (CT-scans, biology, FDG-PET), and a little curiosity left about this peculiar disease and a global approach of the patient should allow even better results in the long-run than those observed so far.

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Manuscript processing

Manuscript received April 14, 2003; accepted September 10, 2003.