Guidelines for management of Pediatric Hodgkin Lymphoma

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1.0 Introduction and Background

Although a significant number of children are diagnosed with Hodgkin lymphoma, by far the majority of cases occur in the adult age group. In the United States of America the Seer Data reports the median age of diagnosis at 38 years and only 3.2% of all Hodgkin lymphoma diagnoses occur in children under the age of 15 years. (1) A further 15% of patients fall within the adolescent/young adult age group, while the remaining 81.8% of the Hodgkin lymphoma diagnoses fall beyond 24 years of age. Similar age related incidence rates are available in data from Europe. (2) The National Cancer Registry for Saudi Arabia reports that in 2004 Hodgkin lymphoma constituted 11.8% of all pediatric (<14 years old) malignancies. (3) This certainly makes children a significant minority among the patients with HL.

Due to the much higher prevalence of HL in adults treatment strategy for childhood HL has followed therapy utilized in adults. In the 1960s, the primary treatment for localized disease was radiation therapy, and with the development of MOPP chemotherapy, advanced stage disease patients were found to benefit with the addition of MOPP to radiation therapy (XRT). By the 1970s most oncologists had adopted the multi-modality therapy model and were treating pediatric patients with MOPP plus XRT for all stages of disease. The 1980s saw a realization of the high rate of long-term toxicity associated with the treatment of children with this strategy and the ABVD protocol was adopted as the potentially less toxic replacement for MOPP. From the 1990s onwards there has been an effort to determine subgroups where there can be further reductions in therapy, either chemotherapy or XRT. While numerous studies have been conducted which have allowed us over time to develop HL treatment strategies, in the ensuing paragraphs I will present the results of a few in order to demonstrate how this occurred.

In 2002 Donaldson et al reported the results of a study that utilized a novel chemotherapy protocol for early stage (stages I and II) HL that had the potential for reducing some of the long term toxicity associated with ABVD. (15) This protocol replaced Bleomycin and Dacarbazine with Methotrexate and Prednisone, producing the VAMP protocol (Vinblastine, Adriamycin, Methotrexate, and Prednisone). XRT was used at much lower doses than previously and was administered on the basis of response evaluation and to a treatment field that included only sites of initial involvement (IF-XRT). Patients who achieved a complete response (CR) following two cycles of VAMP chemotherapy received 1500 cGy, while those who had achieved only a partial response (PR) were given 2550 cGy. All patients then
received the remaining two cycles of chemotherapy following XRT. With a median follow-up of 5.6 years, the 5-year overall survival (OS) and event free survival (EFS) were 99% and 93%, respectively. Early response to the chemotherapy was predictive of outcome with EFS of 100% for those who had achieved a CR following two cycles of chemotherapy as compared to 87% who had not. This study demonstrated two important results; avoidance of alkylating agents, bleomycin, etoposide and high-dose, extended-field XRT was feasible in patients with low-risk disease, and a response-based, risk-stratification strategy could be successful in achieving a high cure rate and reducing toxicity.

Around the same time the Children’s Cancer Group (CCG) in the US reported the results of a clinical trial (CCG5942) that attempted to eliminate radiation therapy in patients with low risk disease. (16) Patients with low risk disease who achieved a complete response following either four or six courses of COPP/ABV hybrid chemotherapy or patients with stage IV HL following intensive multi-agent chemotherapy were randomized to receive either low-dose (2100cGy) involved-field (LD IFXRT) XRT or no radiation therapy. While the OS and EFS for all patients was good (95% and 87% at three years), there was a statistically different outcome for patients who did or did not receive XRT (EFS 93±1.7% v. 85±2.3%; p=0.0024). This resulted in early closure of the study, with the conclusion that radiation therapy, albeit LD IFXRT, even after complete response to chemotherapy was required. They did, however, state that this addition of XRT did not confer a survival advantage at this short follow-up time point.

In the 2008, at the 10th International Congress on Malignant Lymphoma in Lugano, Switzerland, Dr. Nachman presented an update on these results. (17) At 10-years, the EFS and OS for all patients remained acceptable at 83.4±1.3% and 92.5±1.0%, respectively. Even at this time-point while there remained no difference in the OS for patients who had received XRT compared to those who had not, the difference in the EFS between the two groups continued to be significantly different favoring those who had received XRT (91.2% v. 82.4%; p=0.004). The initial conclusion was the same as that made six years earlier, supporting the use of XRT in patients who achieve a complete response to chemotherapy. However, as there was no survival advantage to XRT, it is clear that for every 100 patients irradiated nine relapses are prevented. If XRT were a relatively non-toxic modality one could be safe in recommending its use for all patients, however due to the potential long-term effects more study has to be undertaken to identify smaller subsets of patients who may benefit more from the XRT. Further analysis showed a significantly worse
remission rate for patients with nodular sclerosis subtype compared to mixed cellularity and lymphocyte predominance disease. Also, there was a higher risk of relapse in those patients with NS histology who received only chemotherapy. Inclusion of any other clinical poor risk feature (B-symptoms, bulk disease or ESR>20) to patients with NS histology identified a subgroup who benefited from XRT even if they achieved CR to chemotherapy. Therefore, they recommended that XRT would be beneficial to patients with any histology who did not achieve CR to chemotherapy alone and to patients with NS histology who had additional clinical risk factors.

Further evidence that a subset of HL patients could be treated without XRT came from the Memorial Sloan Kettering Cancer Center. (18) They randomized low risk patients (stages I, II and IIIA; non bulky) to receive six cycles of ABVD with or without XRT (3600cGy), and showed equivalent survival rates (OS and EFS) for both groups of patients.

Our own group at the King Faisal Specialist Hospital and Research Center (KFSHRC) in Riyadh, Saudi Arabia, has also treated HL patients with ABVD with or without XRT. The decision to irradiate was left to the primary treating physician, but generally was administered to patients with clinical risk factors (bulky disease; mediastinal mass) or those with a slow response to therapy (persistence of clinically evident disease following two or three cycles of ABVD). All attempts were made to avoid XRT in patients less than five years old at the time of diagnosis. 153 patients treated between 1997 and 2004 had an OS at five years of 96.7% and an EFS of 86.7% (Figure 1).
Figure 1: Overall survival (A: 96.7% at 5 years) and Event Free survival (B: 86.7% at 5 years) for 153 pediatric patients treated for Hodgkin’s lymphoma at the King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, with ABVD ± XRT.

Of 118 low risk patients (stages I, II and IIIA), 40 were treated with chemotherapy alone while 78 received additional XRT; 66 patients achieved a CR to chemotherapy and received 1500cGy while 12 patients received between 1655 and 3500cGy for residual disease at the end of scheduled chemotherapy (stages I-II received 3-4 cycles; stage III received 6 cycles). The OS for this group of low-risk patients was 99.1% at five years with an EFS of 89.9%. While the OS for patients who received combined modality therapy (CMT) was similar to those patients who received only chemotherapy (98.7% v. 100%; p=0.3; Figure 2A), the EFS was somewhat higher for
those who received only chemotherapy (87.3% v. 95%; p=0.3; Figure 2B), although this was not statistically significant. This slightly higher rate of relapse for patients who received CMT is likely related to the higher risk status for this group of patients.

Figure 2: Outcome of low risk patients (stages I, II and IIIA) treated with chemotherapy alone or with additional radiation therapy. The 5-year OS and EFS for all 118 patients is 99.1% and 89.9%. OS (A) for patients who were treated with chemotherapy v. CMT is 100% and 98.7% (p=0.3), respectively. EFS (B) for these patients is 95% and 87.3% (p=0.3), respectively.

Treatment for patients with advanced stage disease is complicated by the worse outcomes in spite of the more intensive therapy generally administered to these patients. The requirement for more multi-agent, intensive and consequently more toxic chemotherapy has to be balanced against the need to use radiation therapy. In addition the optimal dose of XRT and the radiation field also remains controversial.
While IF-XRT is practical and becoming standard of care for low-stage patients, even IF-XRT in patients with disseminated disease could involve irradiation to extensive areas. Using various chemotherapeutic regimens investigators have achieved overall survival results in the range of 82% to 97%. (19; 20; 21; 22) Head-to-head comparison of the regimens, however, did indicate a poorer outcome for the Stanford V protocol when compared to two other chemotherapy regimens. (19) The OS and FFS for patients treated with ABVD and MOPPEBVCAD in this study were similar (OS: 90% and 89%; FFS: 78% and 81%, respectively), while there were significantly more treatment failures in the Stanford V arm (FFS 54%; p<0.1). Radiation therapy in this study was administered only to those patients who failed to achieve an unequivocal CR or had bulky disease at presentation (59% of all patients).

In this context, it seems that the somewhat gentler Stanford V chemotherapeutic regime requires the addition of XRT in order to maintain optimal efficacy. (20) On the other hand, while failure from progression was best achieved with the intensive, multi-agent MOPPEBVCAD protocol, this also resulted in the highest incidence of hematological toxicity, deaths in CR and second malignancies. Two other studies that tested the elimination of XRT in patients with advanced stage HL further complicate the issue. While the POG 8725 study, which used an alternating MOPP/ABVD chemotherapy regimen, failed to show an additional benefit of total nodal XRT, (22) the GPOH-HD 95 study demonstrated a higher incidence of treatment failure with their multi-agent (OEPA/OPPA + COPP) regimen when radiation was withheld. (21) Clearly, the need for XRT should be determined by the chemotherapeutic regimen used and generalized recommendations regarding the requirement or not of XRT should be avoided. Intensification of chemotherapy should also be considered judiciously as the toxicity of therapy may be different in children as compared to adults. This was clearly suggested when the BEACOPP regimen, which is gaining standard therapy status in adult advanced stage disease, was tested in the pediatric population. (23) While early tumor control was excellent, there was an increase in the incidence of typhlitis resulting in one death, suggesting higher regimen-related toxicity in children as compared to adults.

At our institution we have opted to treat our patients primarily with chemotherapy using the ABVD regimen. 35 patients were classified as advanced stage (stages IIB, IIIB, IV). Twenty-nine patients received the target treatment of six cycles of ABVD; one received eight cycles, four progressed on therapy following 2.5-4 cycles and one suffered an early death following the first cycle. Fifteen patients received XRT; 13 to a dose of 1500cGy and two with residual disease following chemotherapy received
1800cGy and 2550cGy. There were eight treatment failures with four relapses and four had disease progression. The OS at five years was 88% with an EFS of 77%.

Special consideration has to be given to the very youngest group of children. Our group has reported the clinical characteristics of these very young children, showing a higher male preponderance, and lower incidence of poor risk features such as bulky disease and mediastinal involvement when compared with older children. (14) The United Kingdom Children’s Cancer Study Group (UKCCSG) reported on their experience with treatment of these very young patients, reporting outcome for a cohort of 81 patients treated on two consecutive UKCCSG protocols (HD1 and HD2). (24) Twenty four patients (all limited stage disease) were treated with XRT alone and slightly over one-third of the total patients received XRT. While the survival for this group was acceptable, there was a worryingly high incidence of relapse in the patients with stage I disease. Also, toxicity related to the XRT was common and severe. Our own treatment strategy for these children has focused on the avoidance of XRT. Only 20% of our 69 patients were treated with XRT and the majority of these received a very low dose (1500 cGy). Treatment outcome for these patients was no different from the older children and no XRT-related toxicity has been documented so far.

The availability of newer modalities of functional imaging techniques that allow determination of tumor viability following therapy has resulted in more emphasis on treatment stratification based on response evaluation. FDG-PET examination of chemotherapy response following two cycles of therapy has been shown to be highly predictive of outcome. Patients who achieve a complete response at this time-point can be expected to have a high chance of cure even with minimal therapy and can avoid XRT.

Our experience with the ABVD chemotherapy protocol, administered either alone or with minimal dose and field of radiation, provides us with the basis for our new treatment strategy for patients with HL. In addition the availability of functional scanning with the FDG-PET CT scan provides us with the necessary tool to risk stratify these patients and use risk-based therapy. Such a strategy will allow us to provide adequately intensive therapy to patients who need it, while avoiding excessive treatment for those who can be treated with less. Certainly toxicity, particularly long-term toxicity, of chemo- and radiation-therapy would be reduced with this methodology.
2.0 Diagnostic Workup

The following studies need to be conducted on all patients prior to completion of diagnostic workup and initiation of therapy:

- Detailed history including past medical history, family history and immunization history
- Physical examination
- Complete Blood Count with differential
- Erythrocyte sedimentation rate (ESR)
- Serum electrolytes and renal function studies including creatinine and blood urea nitrogen (BUN)
- Hepatic function studies including total and direct bilirubin, alanine aminotransferase (ALT) and albumin.
- Serum calcium, magnesium, phosphate
- Serum uric acid
- Serum lactate dehydrogenase (LDH)
- Quantitative glucose 6 phosphate dehydrogenase (G6PD) levels
- Varicella IgG
- PT/PTT
- EBV panel
- Chest x-ray
- Echocardiogram
- Excisional biopsy of a representative lymph node. Patients who have already undergone an excisional lymph node biopsy at the referring hospital do not necessarily need to have a repeat biopsy. All effort needs to be made to procure the biopsy sample (slides and paraffin blocks) from the referring hospital. These should be submitted to the Department of Pathology and Laboratory Medicine for review and diagnosis. If such a specimen is unavailable or the sample is deemed non-representative or poor quality after pathologist’s review, a repeat excisional biopsy should be undertaken. *Fine needle aspiration (FNA) biopsy should only be done under extenuating circumstances when the option of excisional tissue does not exist.*
- CT scan of the head and neck, chest, abdomen and pelvis. Additional body sites should be included in the CT scan if there is clinical suspicion of involvement with the lymphoma.
- FDG-PET CT scan should be done prior to initiation of therapy for all patients. Results of the FDG-PET CT scan do not need to be available prior to starting
chemotherapy, however, these results must be reviewed as soon as available in order to confirm stage and determine the extent of therapy.

- Skeletal survey and bone scan should be performed in patients who have suspicion of boney involvement, such as bone pain or tenderness, or elevated alkaline phosphatase levels. This is particularly important in those patients who have a negative FDG-PET scan.
- Bone marrow aspirate and biopsy is not necessary for all patients. However, it is essential for the following patients:
  1) those who are stage IV by other criteria
  2) all patients with B-symptoms
  3) patients with extensive stage III disease (III₂)
  4) patients with cytopenias on peripheral blood examination
  5) patients with WBC count >15 x 10⁹/L

Patients who have a negative bone marrow result, but have evidence of bone/bone marrow involvement on FDG-PET scan will be considered bone marrow positive.

### 3.0 Pathological Classification

Pathological diagnosis of Hodgkin’s lymphoma should be made by review of tissue derived from tissue rather than cytology. Diagnosis should be pathologically categorized and recorded as below:

<table>
<thead>
<tr>
<th>Hodgkin Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Subtype</strong></td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Table 1: Histopathological classification of Hodgkin Lymphoma**

When Classical Hodgkin’s lymphoma cannot be subtyped, this should be clearly denoted as “Unclassified”.

4.0 Staging

The disease should be staged using the modified Ann Arbor staging system as outlined below.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (I_E).</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (II_E).</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by involvement of the spleen (III_S) or by localized involvement of an extralymphatic organ or site (III_E) or both (III_ES).</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node involvement.</td>
</tr>
</tbody>
</table>

*Note:* The absence or presence of unexplained fever higher than 38°C for 3 consecutive days, drenching night sweats, or unexplained loss of 10% or more of body weight in the 6 months preceding presentation are to be denoted in all cases by the suffix A or B, respectively.

**Table 2: Ann Arbor Staging Classification of Hodgkin’s Lymphoma.**

Details of the lymph nodal regions are depicted in Figure 3. Laterality is utilized in defining the stage when the following regions are involved and should be denoted with “right” or “left” categorization:

- Cervical, supraclavicular, occipital and pre-auricular.
- Infracavicular.
- Axillary and pectoral.
- Epitrochlear and brachial.
- Hilar.
- Iliac.
- Inguinal and femoral.
- Popliteal.
Further categorization of abdominal involvement to “upper” and “lower” abdomen is depicted in Figure 4. This is denoted with a subscript 1 or 2, respectively, following the major A or B categorization, e.g. IIIA_1 for a patient with stage III disease involving the spleen and the upper abdominal lymph nodes.
4.1 Bulky Disease

Bulky disease is defined as:

- A single lymph node greater than 5 cm in diameter
- A conglomerate mass of nodes greater than 7 cm in diameter
- Mediastinal widening as determined by an AP plain chest X-ray. Mediastinal disease is considered bulky if the measurement of the widest segment of the mediastinum is greater than one-third of the internal diameter of the chest taken at its widest point.

5.0 Risk stratification

At initial evaluation, patients will be stratified into two risk groups:

- **Low risk:** all patients with stages I, II and III₁ or III₂. These patients should have no B symptoms.
- **High risk:** all patients with B-symptoms and those with stages III₂ and IV.

Bulky disease or mediastinal involvement will not be taken into consideration when determining risk.
Further risk stratification will be determined by the response to chemotherapy as defined by resolution of FDG activity following two cycles of chemotherapy.

6.0 Treatment strategy

All patients will receive two cycles of ABVD protocol therapy following completion of diagnostic and staging workup. Response evaluation at this time will determine subsequent therapy.

6.1 Low stage

- **Complete response**
  - ABVD 1 → ABVD 2 → CT-PET → ABVD x 2; no XRT

- **Incomplete response**
  - Involved field, low dose (1500 cGy) XRT to sites of slow response
  - Involved field, (2250 cGy) XRT to sites of slow response
6.2 High stage

ABVD 1 → ABVD2 → CT-PET → Complete response → ABVD x 4; No XRT

Incomplete response → ABVD x 4 cycles

Repeat CT-PET after completion of all 6 cycles

Complete response

Involved field
XRT 1500 cGy

Incomplete response

IFXRT 1500 cGy to sites of delayed response; 2250 cGy to sites of residual activity

Patients with evidence of disease progression at any time point, either clinically or radiologically, will be considered as having failed therapy and should receive alternative/second-line therapy.
7.0 Chemotherapy

7.1 ABVD

Each cycle of ABVD lasts for 28 days, with chemotherapy administered on Days 0 and 14.

- Adriamycin 25 mg/m² IV administered on Days 0 and 14
- Bleomycin 10 units/m² IV administered on Days 0 and 14
- Vinblastine 6 mg/m² IV administered on Days 0 and 14
- Dacarbazine 400 mg/m² IV administered on Days 0 and 14

Prior to each dose of chemotherapy (Day 0 or Day 14) the absolute neutrophil count (ANC) must be greater than 500 x 10⁶/L and the platelet count must be greater than 75 x 10⁹/L. Granulocyte colony stimulating factor (G-CSF) can be used at the treating physician’s discretion in order to maintain the every two week timing for chemotherapy administration.

8.0 Management of toxicity

8.1 Hematological toxicity

The most commonly encountered hematological toxicity on this protocol is leucopenia and neutropenia. For most patients this is self resolving and does not impact on the administration of subsequent doses of therapy. However on occasion this may be more prolonged and could result in delay in administration of the subsequent cycle of therapy. In such patients granulocyte colony stimulating factor (GCSF) may be used at a dose of 5 mcg/kg/dose at a schedule that is decided upon by the treating physician.
8.2 Hepatic toxicity

Doxorubicin and vinblastine doses should be modified for hyperbilirubinemia according to the following criteria:

<table>
<thead>
<tr>
<th>Direct bilirubin</th>
<th>Dose reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25 μmol/L</td>
<td>Full Dose</td>
</tr>
<tr>
<td>25-50 μmol/L</td>
<td>50%</td>
</tr>
<tr>
<td>51-85 μmol/L</td>
<td>75%</td>
</tr>
<tr>
<td>&gt;80 μmol/L</td>
<td>Hold dose</td>
</tr>
</tbody>
</table>

> 85 μmol/L - Withhold dose until toxicity resolved. Do NOT make up missed doses.
If elevation persists > 1 month, exclude infectious hepatitis or other causes of hyperbilirubinemia.

8.3 Cardiac toxicity

Discontinue doxorubicin for clinical or echocardiographic evidence of cardiomyopathy (shortening fraction (SF) < 27% or left ventricular ejection fraction (LVEF) < 50%). Doxorubicin should not be routinely administered to such patients who have developed cardiac toxicity.
8.4 Neurological toxicity

**PERIPHERAL NEUROPATHY:** Neuropathy should be documented using the scale provided below.

<table>
<thead>
<tr>
<th>Modified “Balis” Pediatric Scale of Peripheral Neuropathies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MOTOR NEUROPATHY</strong></td>
</tr>
<tr>
<td>Grade 1</td>
</tr>
<tr>
<td>Grade 2</td>
</tr>
<tr>
<td>Grade 3</td>
</tr>
<tr>
<td>Grade 4</td>
</tr>
<tr>
<td><strong>SENSORY NEUROPATHY</strong></td>
</tr>
<tr>
<td>Grade 1</td>
</tr>
<tr>
<td>Grade 2</td>
</tr>
<tr>
<td>Grade 3</td>
</tr>
<tr>
<td>Grade 4</td>
</tr>
</tbody>
</table>

**SEVERE NEUROPATHIC PAIN (≥ GRADE 3):** Hold dose(s). When symptoms subside, resume at 4 mg/m², and then escalate to full dose as tolerated. Drugs such as gabapentin may be of value. If severe consider evaluation for Charcot Marie Tooth Disease (CMT), type 1A or hereditary neuropathy with liability to pressure palsies. Ask family history.

**VOCAL CORD PARALYSIS:** Hold dose(s). When symptoms subside, resume at 4 mg/m², and then escalate to full dose as tolerated.

**FOOT DROP, PARESIS:** Should be grade 3 to consider holding or decreasing doses. Physical therapy may be beneficial to maintain range of motion and provide AFO’s and other forms of support. Gabapentin may be of value.

**JAW PAIN** – Treat with analgesics, DO NOT modify vinblastine dose.
8.5 **Pulmonary toxicity**

Pulmonary fibrosis is a serious risk with the use of Bleomycin. However, although it may occur, pulmonary toxicity below a cumulative dose of 150 units/m$^2$ is rare. The cumulative dose on this protocol is 80 units/m$^2$. Nonetheless, patients experiencing dry cough, dyspnea, rales and pulmonary infiltrates should be evaluated for potential pulmonary toxicity at any cumulative Bleomycin dose, as a distinct hypersensitivity pneumonitis is recognized at any dose. Patients with the above signs and symptoms should be evaluated by the pulmonology service and should undergo pulmonary function studies. Patients with documented pneumonitis should be treated with corticosteroids and should not receive any further doses of Bleomycin.

8.6 **Nausea and vomiting**

Doxorubicin and Dacarbazine are both highly emetogenic agents. In addition there is an incidence of delayed emesis with these agents. All patients should receive either ondansetron or granisetron and dexamethasone intravenously prior to the chemotherapy. Patients should also receive oral antiemetic agents (ondansetron) for 24- to 48-hours following the chemotherapy. Longer duration of antiemetic therapy may be required in a few patients.

9.0 **Off therapy evaluations**

9.1 **Imaging studies**

All patients should have CT scan evaluation of the sites of initial involvement at the end of therapy. For patients who have received only chemotherapy this can be performed within the first 2 months following the last dose of chemotherapy. For patients who have received radiation therapy either for slow initial response or for residual disease at the end of therapy should have CT-PET scan evaluation of the sites of initial disease between 4 and 6 weeks following the end of the course of radiation therapy.
Patients who have achieved a complete radiological response to therapy will be followed by imaging studies according to the schema below:

<table>
<thead>
<tr>
<th>Months after completion of therapy</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
<th>54</th>
<th>60</th>
<th>72</th>
<th>84</th>
<th>96</th>
<th>108</th>
</tr>
</thead>
<tbody>
<tr>
<td>US abdomen</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>x</td>
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Any abnormalities on these imaging studies suspicious of recurrence will be evaluated further by CT-PET.

9.2 Echocardiogram
All patients will undergo an echocardiogram at the end of therapy. Patients with a normal cardiac function at this time point will henceforth be evaluated by an echocardiogram once every year. Patients with abnormalities on any cardiac evaluation may require more frequent or different evaluations, according to the treating physician’s judgment.

9.3 Blood tests
Routine blood tests will be conducted at each follow-up clinic visit. These routine tests include complete blood count with differential (CBCD), renal profile (creatinine and electrolytes), hepatic profile (ALT, total bilirubin, albumin) and erythrocyte sedimentation rate (ESR). In addition all patients should also be tested annually for thyroid function with thyroid stimulating hormone (TSH) and total T4.

9.4 Pulmonary Function Tests
Pulmonary function studies should be conducted on all patients within 6 months off therapy and then once every other year. Frequency of testing would change if there is any change in clinical status or alterations in the study results.