Study protocol

Phase II Trial to assess the Efficacy of Low Radiation Dose of 20 Gy for the Treatment of Marginal Zone Lymphoma or Follicular Lymphoma Stage I-II localized in the Stomach or the Duodenum

ISRT 20 Gy in Localized Indolent **G**astric or **D**uodenal **L**ymphoma
(GDL-ISRT 20 Gy)

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Amendments and Updates

Number	Date	Amendment or Update	Reason
1	25.11.2019	Amendment	1. Additional Staging with PET-CT 2. Advanced duodenal NHL St. II2E can be treated with abdominal ISRT 4 Gy 3. Minimal Residual Disease (MRD) Diagnostics (Liquid Biopsies) with University UKSH, Kiel
2	09.03.2020	Amendment	1. MR linac permitted 2. Breath-hold radiation technique is allowed (instead of 4D-CT) 3. Work up / follow-up details. 4. Blood collection within research project is optional
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Prof. Dr. med. H.Th. Eich/ Dr. med. Gabriele Reinartz

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Statistician:
Kiana Kreitz/ Jeanette Köppe

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Place, date

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Signature

I have read this study protocol and agree to conduct this study in accordance with all stipulations of the study protocol and in accordance with the Declaration of Helsinki.

Investigator:

Prof. Dr. med. H.Th. Eich

Name	**Place, date**
	Signature

Dr. med. Gabriele Reinartz

Name	**Place, date**
	Signature

1.3 Synopsis

Title:	Phase II Trial to assess the Efficacy of Low Radiation Dose of 20 Gy for the Treatment of Marginal Zone Lymphoma or Follicular Lymphoma Stage I-II localized in the Stomach or the Duodenum
Short Title:	ISRT 20 Gy in Localized Indolent **G**astric or **D**uodenal **L**ymphoma
Acronym	GDL-ISRT 20 Gy
Protocol version identifier:	01, 23.08.2020
Register-No.	NCT04097067 (ClinicalTrials.gov)
Lead Investigators:	Prof. Dr. med. H.Th. Eich/ Dr. med. G. Reinartz
Indication/ Medical condition:	Primary indolent (marginal zone or follicular) gastric or duodenal lymphoma
Study Design:	Prospective single-arm multicenter study
Active substance/ Medicinal product	None
Intervention(s):	Involved Site RadioTherapy (ISRT) with 20 Gy
Treatment plan	-Study enrollment, **blood draw** for **biomarker-analysis** (at baseline visit/ after 4 Gy/ after 10 Gy / after 20 Gy RT/ at 3 and 6 months after RT) -CT-based planning of RT -**ISRT** with **IMRT** (oder 3D-CRT)**/ IGRT, daily 2 Gy ad 20 Gy**
Objectives:	-Prove the effectiveness of 20 Gy and non-inferiority to 30 Gy with respect to response rate. -Recording of survival rates, quality of life (QoL), radiogenic toxicities and inflammation relevant molecules. *-Primary Objective*: Response rate 6 months after end of treatment, 4 categories according to GELA-criteria: CR (complete remission) = CR or pMRD (probable minimal residual disease), PR (partial remission) = rRD (responding residual disease), NC (no change), PD (progressive disease) *-Secondary Objectives:* QoL according to EORTC (QLQ C30 and STO22). EFS=Event-free survival (time to any failure or death from any cause, all patients), PFS=Progression-free survival (time to progression of lymphoma or death from any cause, patients in PR or SD), RFS=Recurrence-free survival (time to recurrence of lymphoma or death from any cause, patients in CR), LSS=Lymphoma-specific survival (time to death related to lymphoma or associated with the treatment, all patients), OS=Overall survival

	(time to death from any cause, all patients). Level of cytokines IL-1β, IL-4, IL-8, TNFalpha and other inflammation relevant molecules Syndecan1, MMP-2 and S100 proteins. Acute toxicities during treatment according to NCI-CTC, chronic toxicities according to NCI-CTC/ LENT-SOMA. Monitoring of Adverse Events (AEs) and Serious Adverse Events (SAEs) -Assessment of safety: Monitoring of Adverse Events (AEs) and Serious Adverse Events (SAEs)
Inclusion Criteria:	-primary indolent gastric or duodenal lymphoma -pathology: marginal zone lymphoma (MZL) or follicular lymphoma (FL) -stage: clinical stage I or II (Ann Arbor classification) -H. pylori negative or antibiotic resistant lymphoma -any FLIPI score low – high (0-4) -any size of tumor or affected lymph nodes -male or female with age ≥ 18 years -performance status ECOG 0 – 3 -written informed consent by the patient
Exclusion Criteria:	-prior radiation treatment of the gastrointestinal lymphoma -stage: clinical stage III or IV (Ann Arbor classification)-unability to understand the informed consent or unwillingness to participate in the study -severe comorbidity or organ dysfunction contraindicating the use of RT (liver cirrhosis Child-Pugh C, chronic obstructive pulmonary disease GOLD 4, heart insufficiency NYHA IV, dialysis dependent renal insufficiency, uncontrolled epilepsy) -known seropositivity for HIV -acute hepatitis B or C infection -chronic inflammatory bowel disease -prior malignant disease (exclusion: basalioma, non-metastasized solid tumor in constant remission diagnosed >3 years ago) -pregnancy or breastfeeding -active substance abuse or severely compromised compliance
Statistical Methods:	Primary endpoint analysis: The primary endpoint is the overall response rate (ORR) 6 months after end of treatment. It will be analysed by a one-sample non-inferiority binomial test. The one-sided significance level is 2.5%, the power is 80%. It will be tested whether ORR will be non-inferior to 0.95, with non-inferiority margin (difference) 0.1, i.e. it will be tested whether the lower limit of the one-sided 97.5% confidence interval by Clopper-Pearson will be greater than 0.85. Secondary endpoint analysis: The pre-specified secondary endpoints will be analysed with appropriate statistical methods depending on the type of variable, e.g. rates are analysed by binomial test and exact 95%-confidence interval, time-to-event endpoints by one-sample log-rank test.
Number of Patients/ Sample size:	**To be assessed for eligibility:** n = 88 **To be assigned to the trial:** n = 83 **To be analyzed:** n = 79

Participating Centers:	University Hospitals of: Beijing, Essen, Heidelberg, Kiel, Gießen-Marburg, Muenchen LMU, Muenchen TU, Muenster, New York MSKCC, Rochester, Singapore, Tokyo, Torino, Tuebingen, Boston, San Francisco, Toronto. Other expert hospitals: Bielefeld Franziskus Hospital, Mönchengladbach Kliniken Maria Hilf. Participating (Inter-) national centers after approval of their Ethics Committee/ Institutional Review Board.
Trial duration /Schedule:	Planned recruitment duration: 1.5 years Duration of single patient participation: RT intervention of two weeks plus 6 months after end of treatment Planned overall duration of the study: 2 years Planned start of recruiting/data collection: September 01, 2019 Planned end of data collection: (August 31, 2021) Under the impact of the COVID 19 pandemic the study period will be extended by 6 months until February 28 2022. Planned final report of study results: (August 31 2022) February 28 2023.
Visits:	Visits summary: Baseline visit, first day of RT treatment, second day (after 4 Gy), 5th day of RT (after 10 Gy), last day of RT (after 20 Gy), 6 weeks after end of RT±5 d, 3 and 6 and 9 months after end of RT±3 weeks, 1 year after end of RT±3 weeks, 2 years after end of RT±3 weeks.
Financial Support:	An application for funding was submitted to the IZKF Muenster and to the DLH-foundation.

1.4 Abbreviations

AE	Adverse Event
ARO	Arbeitsgemeinschaft Radiologische Onkologie
BBB-approach	Bench-Bedside-Bench-approach
CT	Computed tomography
CTC	Common Toxicity Criteria
CTV	Clinical Target Volume
DMC	Data Monitoring Committee
DSGL	German Study Group Gastrointestinal Lymphoma (Deutsche Studiengruppe Gastrointestinale Lymphome)
DVH	Dose Volume Histogram
ECOG	Eastern Cooperative Oncology Group
(e)CRF	(Electronic) Case Report Form
EFS	Event-free survival
ENT	Ear Nose Throat
EORTC	European Organization for Research and Treatment of Cancer
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GDL	Gastric or Duodenal Lymphoma
GI	Gastrointestinal
GTV	Gross Tumor Volume
Gy	Gray
H.p.	Helicobacter pylori
ICRU	International Commission on Radiation Units and Measurements
IGRT	image guided radiotherapy
ILROG	International Lymphoma Radiation Oncology Group
IMRT	Intensity Modulated Radiotherapy
IPI	International Prognostic Index
IRB	Institutional Review Board
ITV	Internal Target Volume
ISRT	Involved Site Radiotherapy
LN	Lymph Node
LSS	Lymphoma-specific survival
MALT	Mucosa Associated Lymphoid Tissue
MZL	Marginal zone lymphoma
MRD	Minimal Residual Disease
NHL	Non-Hodgkin lymphoma
OS	Overall survival
PET	Positron Emission Tomography
PFS	Progression-free survival
PTV	Planning Target Volume
QoL	Quality of Life
QUANTEC	Quantitative Analysis of Normal Tissue Effects in the Clinic
RFS	Recurrence-free survival
RT	Radiotherapy
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction

2 Introduction

2.1 Background Information and Rationale

Primary gastrointestinal lymphomas are rare tumors with an incidence of 0.1-1/100,000 per year. Extranodal indolent lymphomas comprise different histologic subtypes e.g. as marginal zone lymphoma (MZL) or follicular lymphoma (FL). Extranodal MZL most frequently (66%) are located in the gastrointestinal tract, and involvement of the stomach accounts for 30%. Gastrointestinal MZL show low cause-specific mortality rates, they are less likely to relapse than non-gastrointestinal extranodal MZL. MZL often arise multifocally within the stomach. Bowel cases of gastrointestinal FL are most common (63%), followed by gastric cases (18%). Bowel cases of FL have better outcomes (5-year OS = 81%, p<0.001) in comparison to gastric FL cases (5-year OS = 53%). Gastrointestinal lymphomas (GIL) represent a low risk of distant dissemination.
Actual guidelines on gastrointestinal indolent lymphoma favour an organ-preserving approach. The standard treatment of Helicobacter pylori (HP) positive gastric lymphoma is an antimicrobial therapy. In case of persisting lymphoma after HP eradication and in case of HP-negative lymphoma patients are treated with local radiation therapy with curative intent. For indolent lymphoma of the bowel surgical treatment is limited to rare complications (perforation or bleeding). Depending on the primary localization and extent of the disease uncomplicated indolent lymphomas of the bowel are treated with local (NHL confined to duodenum) or locoregional "whole abdominal" (NHL of the small bowel or duodenal lymphoma with confirmed/ suspected involvement of small bowel) radiation therapy.
For extranodal indolent Non Hodgkin lymphoma regardless of the localization the radiation dose range is currently reported between 20 and 30 Gy (Lowry 2011). The actual guidelines of the International Lymphoma Radiation Oncology Group (ILROG) for radiation dose given to extranodal indolent non Hodgkin lymphoma (NHL) by Involved Site Radiotherapy (ISRT) are 24-30 Gy depending on the diseased organ, for gastric and duodenal lymphoma 30 Gy are recommended (Yahalom 2015).
As known from previous publications, radiation doses of ≥ 20 Gy do not impair tumor control in indolent NHL. In a retrospective series of 496 irradiated patients from Toronto (1967-1978), the radiation doses applied to fields of involvement were subgrouped in the range from < 20 Gy up to > 40 Gy. Radiation dose did not exert a significant effect upon local tumor control particularly in low grade lymphoma. For the included 143 patients with localized low grade lymphoma (nodal and/ or extranodal sites) the analysis of outcome by radiation dose failed to indicate a dose-control relationship in the range from 20 to 40 Gy. Dose-response reached a plateau at 20 Gy for indolent non Hodgkin lymphoma with an increase of relative risk of relapse in the subgroup of <20 Gy (Sutcliffe 1985). In a current large multicenter randomized controlled trial (United Kingdom) lower RT doses of 24 vs. 40-45 Gy showed no loss of efficacy in patients with indolent non Hodgkin lymphoma of various sites (predominantly follicular and marginal zone) regarding ORR/ in-field progression/ PFS/ Overall survival (Lowry 2011). International publications keep showing an obvious tendency towards lower radiation doses in extranodal indolent non Hodgkin lymphoma (NHL) of various sites. The multicenter randomized 4 Gy vs. 24 Gy FORT trial at 614 manifestations of indolent NHL (including FL n=469, MZL n=72) has been shown 4 Gy to be effective but resulting in significant lower tumor control in FL, whereas a clear but not significant difference between 4 and 24 Gy resulted for the small subgroup ofMZL (Hoskin 2014).
Extranodal MZL of the stomach are significantly less likely to relapse or progress, compared with primaries in other extraintestinal organs (Teckie 2017). Extranodal FL of the duodenum

are associated with better progression-free survival (PFS) than those of other parts of the GI-tract (Harada 2016).
For indolent gastric lymphoma in the literature of the past 25 years efficient radiation doses of 20-46 Gy are documented; 20 Gy achieved complete remission in small patient numbers (Tsang 2001).
Since our current state of knowledge tells us that RT doses from 20 to 40 Gy reach a consistent tumor control in a variety of (extra-)nodal indolent lymphoma, in this trial the effectiveness of 20 Gy will be verified for gastric/duodenal indolent lymphoma in a prospective stratified design using the modern radiation technique ISRT. This trial addresses the research question, if 20 Gy ISRT is not relevantly inferior to the currently recommended standard dose of 30 Gy in GIL of the stomach or duodenum in respect to the remission rate.
A complete or partial response to RT alone with a median dose of 30 Gy was achieved in at least 95% of patients with early-stage extranodal marginal zone lymphoma at different anatomical sites (Tsang 2003, Teckie 2015).
Based on the current findings, that gastrointestinal indolent B-cell lymphoma could develop against the background of an inflammatory microenvironment with proinflammatory cytokines found to be elevated particularly in gastrointestinal FL and MALT lymphoma (Miyata-Takata 2015), and that ionizing radiation therapy can modulate anti-tumor immune responses (Di Maggio 2015), additional analysis of inflammation relevant molecules is projected in this study. Serum levels of certain cytokines and inflammatory molecules will be determined before and after predefined radiation doses and during follow-up (see chapter 3.1.3. Additional Research Program) to be correlated with histologic subtype and tumor control of GI-lymphoma. This multiparametric approach allows to identify potential targets that may affect radiation-response in GI-lymphoma. Additional analysis of inflammation relevant biomarkers – correlation with lymphoma subtype and tumor control after radiotherapy – identification of targets for radiation dose-response, these steps together provide the specific Bench-Bedside-Bench(BBB)-approach of this trial.

2.2 Risk-Benefit Analysis

In terms of eradicating the lymphoma disease with 20 Gy, patients with GIL could be cured within a two-week course of RT with as few as possible side effects (adverse effects of radiotherapy are dose-dependent). In the unlikely event of persisting disease, patients have the safe option of further RT, a renewed radiation dose of 20-30 Gy would be feasible. Large studies conducted in Australia, Germany and the Netherlands particularly in gastric indolent lymphoma were continued with highly effective doses of at median 40 Gy at once.
During the study for each patient the risk-benefit balance will be analyzed.
The appropriate therapy according to the lowest possible RT dose can have substantial influence on the therapy costs as well as on the therapeutic success. The trial design offers the opportunity to define a new standard RT dose for GIL worldwide.
The potential benefit for the participant/patient concerned is great by having low toxicity and short treatment duration as well as the good prospect of cure.

3 Objectives and Endpoints

3.1 Objectives

3.1.1 Primary Objective

The primary objective is to demonstrate the efficacy and safety of the low-dose RT concept with 20 Gy (10x2 Gy). Therefore, the overall response rate (ORR) to radiation treatment is

examined to evaluate whether the interventional administration of 20 Gy is not relevantly inferior to international standard dose of 30 Gy.

3.1.2 Secondary Objectives

The secondary objectives are the recording and analysis of the following criteria: quality of life and survival rates (event-free survival, lymphoma specific survival, progression-free survival, overall survival). During and after radiation treatment the acute and chronic adverse effects, including possible Adverse Events (AEs) and Serious Adverse Events (SAEs) will be collected.
Certain inflammatory cytokines are known to be elevated in patients with low-grade gastrointestinal lymphoma. In addition, cytokine profiles after radiation exposure are dose dependent. The effects of the radiation dose regimen on the production of cytokines (IL-1ß, IL-4, IL-8, TNFalpha) and other inflammation relevant molecules (Syndecan1, MMP-2 and S100 proteins) are to be investigated. Determination of the relationship between radiation exposure, inflammatory response and (complete) remission rate of each gastrointestinal lymphoma subtype is intended in order to optimize and personalize radiation therapy treatment for each patient.

3.1.3 Additional Research Program (Bench-Bedside-Bench-approach)

Serum samples for Research Program are analyzed at the University of Muenster!

The following inflammation related molecules should be quantified in serum samples of patients six times: prior, during (after 4 Gy, after 10 Gy, after 20 Gy) and at 3 and 6 months follow-up visit after radiation treatment. In the radiobiology lab Muenster the cytokines IL-1ß, IL-4, IL-8,TNFalpha as well as the proteins Syndecan1 and MMP-2, in the immunology lab Muenster additionally S100 proteins are tested.
Magnetic Luminex Assay (R&D Systems) will be used to quantify these biomarkers in serum samples in the radiobiology lab at the University Hospital Muenster. Concentrations of S100A8/ S100A9 are quantified by an in-house ELISA.

Blood collection:
-15 - 18 ml blood should be collected by venipuncture using two 7.5 - 9 ml serum monovettes with clotting activator (e.g. Sarstedt, Nümbrecht, Germany; order no: 02.1063.001)
-for clotting of blood, samples should be stored at room temperature for 20-30 minutes.

Serum isolation and storage in the central laboratory of the clinic:
-monovettes should be centrifuged for 10 min. at 1500 x g
-Serum (supernatant) should be aliqoted by pipetting about 1ml of the serum into separate 2 ml cryotubes or 2ml Eppendorf reaction tubes, so that at least 4 serum aliquots are available from each blood withdrawal (attention: to avoid cellular contamination, release of half a centimeter of serum is indicated and pipette should not put deeper than half a centimeter over pellet into the monovette)
Instead of Eppendorf reaction tubes (e.g. Eppendorf, Wesseling-Berzdorf, Germany) also cryotubes (e.g. Diagonal, Muenster, Germany) can be used.
-The aliquots should immediately be stored **at least at -20 °C in a freezer**.
Repeated freeze-thaw cycles should be avoided and the time from blood collection to freezing of serum should not take longer than 40-60 minutes.
-Labeling of serum samples in accordance with the **6 visit dates 'baseline, 4 Gy, 10 Gy, 20 Gy, 3 months, 6 months':**
'Country_center-patient-visit'
->e.g. 'G001-001-baseline' (G=Germany, 001=Muenster, 001=first patient, baseline visit).

For shipment, samples should be put in a fitting small box and placed in a bigger polystyrene box together with about 6kg dry ice. The box should be sealed with adhesive tape.

Each participating clinic stores its serum samples at the longest until the end of patients acquisition. By each center at two different times (in the second half of the first year, and after the end of recruitment) the samples are sent on dry ice to the radiobiology lab in Muenster, and from there are also forwarded to the immunology lab, in each of which the analyses will be carried out.
In the radiobiology lab the serum samples will be analyzed by using Magnetic Luminex Assay as described by the manufacturer (R&D Systems, Minneapolis Minnesota, USA). A detailed assay instruction can be found at https://resources.rndsystems.com/pdfs/datasheets/lxsahm.pdf and https://www.rndsystems.com/products/human-magnetic-luminex-assay_lxsahm#product-datasheets. The measurement takes place on a Luminex analyzer (Luminex LX200). These analyses should be used to measure the concentration of the six defined biomarkers in serum samples of lymphoma patients in relation to 20 Gy radiation treatment.
In the immunology lab additional markers, as S100 proteins, will be quantified.

Biomarker values should be determined prior (baseline visit), during (**after** 4 Gy, **after** 10 Gy) and directly **after** radiation therapy of 20 Gy, and 3 and 6 months after therapy. The quantitative analysis of the selected biomarkers should give information about the efficacy of the (4 Gy/ 10 Gy/) 20 Gy radiation treatment concept to activate inflammatory and immunological relevant processes in relation to oncological disease response and subtype of GI-lymphoma.

Reseach Program – Hypotheses:
-Serum IL-1β, IL-4, IL-8, TNFalpha, Syndecan1, MMP-2 and S100 proteins are elevated in MZL
-Serum IL-8, TNFalpha, Syndecan1, MMP-2 and S100 proteins are elevated in FL
-Antibiotic-resistant H. pylori-positive status of patient is associated with higher elevation of serum-biomarkers than H. pylori-negative status
-Radiotherapy causes directly a radiation dose-dependent elevation of serum-biomarkers in MZL and FL
-The immediate radiogenic elevation of serum-biomarkers is more pronounced in MZL than in FL
-The immediate radiogenic elevation of serum-biomarkers is more pronounced in gastric-NHL than in duodenal-NHL
-The immediate radiogenic elevation of serum-biomarkers correlates directly proportional to tumor control after radiotherapy
-After radiotherapy at follow-up vs. baseline a decrease of serum-biomarkers is shown in MZL and FL
-Post-radiogenic decrease of serum-biomarkers at follow-up vs. baseline is more pronounced in MZL than in FL
-Post-radiogenic decrease of serum-biomarkers at follow-up vs. baseline is more pronounced in gastric-NHL than in duodenal-NHL
- Post-radiogenic decrease of serum-biomarkers at follow-up vs. baseline correlates directly with tumor control after radiotherapy

3.2 Endpoints

3.2.1 Primary Endpoint

-**Overall response rate ORR** (CR+PR) ≥ 95%, 6 months after the end of treatment.

-4 categories of response, according to **GELA-criteria**: **CR** (complete remission) = CR or pMRD (probable minimal residual disease), **PR** (partial remission) = rRD (responding residual disease), **NC** (no change), **PD** (progressive disease)

3.2.2 Secondary Endpoints

-**Quality of life** (QoL) according to EORTC (QLQ C30 and STO22), at baseline visit/ after 20 Gy (=last day of RT)/ 6 months after end of RT.
-**EFS**=Event-free survival (time from beginning of RT to any failure or death from any cause, all patients). Follow-up over 2 years after end of RT.
-**PFS**=Progression-free survival (time from beginning of RT to progression of lymphoma or death from any cause, patients in PR or SD). Follow-up over 2 years after end of RT.
-**RFS**=Recurrence-free survival (time from beginning of RT to recurrence of lymphoma or death from any cause, patients in CR). Follow-up over 2 years after end of RT.
-**LSS**=Lymphoma-specific survival (time from beginning of RT to death related to lymphoma or associated with the treatment, all patients). Follow-up over 2 years after end of RT.
-**OS**=Overall survival (time from beginning of RT to death from any cause, all patients). Follow-up over 2 years after end of RT.
-Level of **cytokines IL-1β, IL-4, IL-8, TNFalpha** and other inflammation relevant molecules: **Syndecan1 and MMP-2** and **S100 proteins** at baseline visit/ after 4 Gy/ after 10 Gy/ after 20 Gy on last day of RT/ at 3 and 6 months after end of RT.
-**Acute toxicities** during treatment, 6 weeks after end of RT, according to NCI-CTC
-**Chronic toxicities** from 3 months up to 2 years after end of RT, according to NCI-CTC/ LENT-SOMA.
-Incidence of **Adverse Events** (AEs) and **Serious Adverse Events** (SAEs), continuously.

4 Study Design

-Single-arm, prospective, open label, interventional, multicenter study.
-Historic data from irradiated patients with indolent gastrointestinal lymphomas serves as a basis for the intended response rate.
-Participation of further international sites with expertise in radiation treatment of gastrointestinal lymphomas after approval of their Ethics Committee/ IRB.
-Number of 79 patients need to be analyzed.
-Justification for 'single-arm design' and for 'non-inferiority limit': the low prevalence of the disease, the limited risk of the study design (because of the option of renewed RT in case of persisting disease) and the benefit in terms of lower risk of adverse reactions due to the lower RT dose of 20 Gy in comparison to standard dose of 30 Gy.

5 Study Sites and Study Population

5.1 Study Site Selection

The data collection is confined to radiooncological therapy centers with a high level of expertise in modern radiation treatment of GIL to ensure a consistent therapeutic standard and complete documentation.
Institutions would need to support the personnel completing the questionnaires.

5.2 Study Population

5.2.1 Inclusion Criteria

-primary indolent gastric or duodenal lymphoma

-pathology: marginal zone lymphoma (MZL) or follicular lymphoma (FL)
-stage: clinical stage I or II (Ann Arbor classification)
-H. pylori negative or antibiotic resistant lymphoma (defined as PD=progressive disease or NC=no change after antibiotic therapy; in case of NC the interval from H.p. eradication to RT is to be ≥ 12 months)
-any FLIPI score low – high (0-4)
-any size of tumor or affected lymph nodes
-male or female with age ≥ 18 years
-performance status ECOG 0 – 3
-written informed consent by the patient

5.2.2 Exclusion Criteria

-prior radiation treatment of the gastrointestinal lymphoma
-stage: clinical stage III or IV (Ann Arbor classification)
-unability to understand the informed consent or unwillingness to participate in the study
-severe comorbidity or organ dysfunction contraindicating the use of RT (liver cirrhosis Child-Pugh C, chronic obstructive pulmonary disease GOLD 4, heart insufficiency NYHA IV, dialysis dependent renal insufficiency, uncontrolled epilepsy)
-known seropositivity for HIV
-acute hepatitis B or C infection
-chronic inflammatory bowel disease
-prior malignant disease (exclusion: basalioma, non-metastasized solid tumor in constant remission diagnosed >3 years ago)
-pregnancy or breastfeeding
-active substance abuse or severely compromised compliance

6 Patient Inclusion, Registration

The announcement and dissemination of the study concept is to be executed via the medical organisations of radiooncologists, internal oncologists and gastroenterologists, and via the medical members of the International Lymphoma Radiation Oncology Group (ILROG).
Patients are recruited in the participating radiooncological centers (with expertise in radiation treatment of gastrointestinal lymphomas) after assignment by medical colleagues, as general practitioners, internists, gastroenterologists or internal oncologists. The therapeutic concept for a possible study patient can be specified in a multidisciplinary tumor conference or in interdisciplinary discussions with medical colleagues.
Patients who are cared for at one of the participating study sites and who are possibly eligible will be invited for study participation. Once written informed consent to participate in the study has been given (s. chapter 13.2), the patient will be assigned a subject identification code as follows: XX – YY (XX represents a unique number identifying the study site, YY is a continuously increasing number which is uniquely allocated to each patient recruited at the respective study site).
The maximum interval between enrollment in this study and initiation of radiation therapy must not exceed 3 months.

7 Investigational product/ Medical procedure

7.1 Radiotherapy for limited stage indolent lymphoma

7.1.1 Simulation/Planning-CT

The recommendations on planning are derived from the respective ILROG-guidelines for extranodal lymphomas (Yahalom 2015):

- planning and treatment should be performed with an empty stomach
- patient should be immobilized in a supine position with elevated arms
- a small amount (< 50 ml) of oral contrast agents should be administered, i.v. contrast agent is recommended in case of suspected lymph node involvement
- CT-scan should be performed before and after administration of oral contrast agent to account for stomach distension
- organ movement should be registered via 4D-CT-scan or fluoroscopy in order to create an ITV

7.1.2 Target volume delineation

The target volume is delineated in a multi-step process according to the ILROG guidelines on ISRT and encompasses the involved gastric or intestinal region and includes the involved lymph nodes, depending on the stage of disease.

7.1.2.1 ISRT stomach

GTV: macroscopic tumor visible on PET, CT or both and pathological enlarged lymph nodes

CTV: GTV+ whole stomach from the esophagogastral junction to beyond the duodenal bulb. The whole wall of the stomach and perigastric lymph nodes, if visible, have to be included. In case of a duodenal wall infiltration, the whole duodenum has to be irradiated. In stage II, all further tumor manifestations are included in the CTV.

ITV: 4D-CT and fluoroscopy are used to account for gastric movements caused by breathing. In lack of these examinations, a margin of 1-2 cm is recommended.

PTV: dependent upon the setup variation, intraabdominal 1 cm around the final ITV is recommended

Organs at risk: kidneys (right/ left), liver, heart, lung (right/ left/ whole lung), small bowel, spinal cord

7.1.2.2 ISRT duodenum

CTV: If the lymphoma is confined to the duodenum, the whole duodenum is included in the RT field. In case of a possible involvement of the small bowel, a „whole abdomen“ technique is utilized to cover the intestine and mesentery. In stage II, all further tumor manifestations are included in the CTV.

7.1.3 Dosage and Technique

All dose specimen according to ICRU 83:

- Megavoltage photon irradiation should be use
- Dose prescription is 20 Gy, respectively in daily fractions of 2 G

- The use of modern techniques like intensity-modulated radiotherapy (IMRT) is encouraged (alternatively conformal RT with a 3D-plan may be used). Optional 4D-CT or PET-CT based plannin
- For all RT plans, a dose volume histogram (DVH) for the target volume and neighbouring organs at risk (liver, kidneys, spinal cord, lungs, heart, small bowel) is compulsory
- verification: IGRT (image guided radiotherapy) with regular, daily is encouraged, conebeam- CT control.

7.1.4 Dose constraints

Dose constraints are defined according to **Q**uantitative **A**nalysis of **N**ormal **T**issue **E**ffects in the **C**linic:

- Kidneys V_{20}< 32%, V_{12}< 55%, mean dose < 18 Gy. In case of unilateral kidney or precedent functional impairment, lower doses may be necessary. In that case, a consultation with the reference radiation oncology is mandatory.
- Liver V_{28}< 33 %, mean dose < 20 Gy. In case of functional impairment (e.g. transaminase elevation, ascites), a consultation with the reference radiation oncology is mandatory.

In the eCRF the following dose parameters are to be documented:
-PTV: V95, V107, D98, D2, Dmean, Dmax
-Kidneys/ liver/ stomach/ duodenum/ small bowel: V10, V5, Dmean
-Heart/ lungs: V5, Dmean
-Body/ spinal cord: Dmax

8 Study conduct and study assessments

	Trial							**post-trial follow-up**		
Visits	**BV**	**IV-1**	**IV-2**	**IV-3**	**IV-4**	**FU-1**	**FU-2 + FU-3**	**FU-4**	**FU-5**	**FU-6 (Final examination)**
	Baseline visit	First day of RT	Second day of RT (**after 4 Gy**)	5th day of RT (**after 10 Gy**)	Last day of RT (**after 20 Gy**)	6 weeks after end of RT ± 5 d	**3 and 6 months** after end of RT ± 3 weeks	9 months after end of RT ± 3 weeks	1 year after end of RT ± 3 weeks	2 years after end of RT ± 3 weeks
Informed Consent	**X**									
Inclusion / Exclusion Criteria	**X**									
Registration	**X**									
Medical history, concomitant diseases	**X**									
Concomitant medication	**X**									
Demographic data	**X**									
Anamnesis	**X**	**X**	**X**	**X**	**X**	**X**	**XX**	**X**	**X**	**X**
Clinical Examination	**X**	**X**	**X**	**X**	**X**	**X**	**XX**	**X**	**X**	**X**
Endoscopy/ Endosonogra	**X X**						**XX XX**		**X X**	**X X**

phy (+ biopsies)										
CT-imaging (Routine Staging and follow-up care)	**X** (+Routine Planning-CT)						only **at 6 months**		**X**	**X**
PET-CT (optional)	**(X)**						**(X)**			
Abdominal ultrasound	**X**									
Quality of life assessment	**X**				**X**		only **at 6 months**			
Blood draw	**X**		**X**	**X**	**X**		**XX**			
Radiation treatment		**20 Gy (two weeks)**								
Adverse **acute** reactions		**X**	**X**	**X**	**X**	**X**				
Adverse **chronic** reactions							**XX**	**X**	**X**	**X**
Adverse events		**X**								
Final examination										**X**

IV=intermediate visit, FU=follow-up

8.1 Screening and baseline visit (bv)

Staging examinations have to be conducted at first to review the requirements for participation in the study. On the basis of endoscopy of the stomach and bowel with histologically proven disease, CT scans of thorax and abdomen for identification of stage, in case of fulfillment of inclusion and lacking exclusion criteria, informed consent of the patient has to be obtained before the start of treatment. The treating oncologist informs the patient in a comprehensible way about his diagnosis, state of the art examinations and therapy as well as the objectives of the study (s. chapter 13.2).
The intended effect and possible side effects of treatment have to be pointed out. It has to be guaranteed that the patient understands his/her free choice to participate in the study, that informed consent may be withdrawn at any time and that the non-participation in the study results in no disadvantages for the patient. In case of consent, the patient has to be aware that data from his/her medical record are drawn for documentation, surveillance of the study and further analysis. The extent and purpose of analyzed data has to be made clear.

Patients should be encouraged to report all medical conditions during and after the RT in possible causality to the treatment to the treating physician. Information on follow-up visits and examinations after treatment have to be given on first contact, the results of which should be transmitted to the study management (see chapter 1.1 study contact).
Permission to anonymous data transfer between participating study sites or further attending physicians and the study management, and data analysis by the study center, is explicitely granted by the patient in the context of his written informed consent in study participation. It also includes the permission for the study center to contact the patient directly or his/her general practitioner in case of missing data to fulfill the study objectives.

Informed consent has to be given in writing and also will be signed by the treating physician.
The patient informed consent form, after signature by the patient and the treating physician (plus witness, if present), will be archived.
Copies of the informed consent and the patient information on the study are given to the patient.

After having signed the informed consent form, patients will undergo anamnesis interview, clinical examination and blood analysis to assess baseline parameters.

A patient must provide written consent before undergoing any protocol-required assessments.

The baseline visit should include the assessment of quality of life with QLQ-C30 and STO-22.

The baseline visit includes blood draw!

The **baseline visit** and the routine (staging) procedures prior to treatment include:

- Anamnesis
  - Symptoms and date of onset
  - B-symptoms
  - Diagnosis and therapy of Helicobacter pylori
  - Medication (especially acid secretion inhibitors and antibiotics) and time of prescription
  - Quality of life assesment of QLQ-C30 and STO-22
- Clinical examination
  - Performance status (ECOG-status)
  - Body weight, blood pressure
  - Palpation of peripheral lymph nodes liver, spleen and abdomen
- Blood analysis
  - Complete blood count
  - LDH, GOT, GPT, alcalic phosphatase, γ-GT, bilirubin, creatinine, protein electrophoresis, total protein, albumin, immunelectrophoresis
  - Serum protein, ferritin, vitamin B12, folic acid (in case of anemia)
  - **Blood draw (at baseline visit):**
    - –**Research program (analyses at the University of Muenster!): Two 7.5 - 9 ml serum monovettes.**
      Centrifugation, freezing and storage see 3.1.3 and Appendix 16.7 (SOP BLOOD SAMPLES for RESEARCH PROGRAM)
      Transmission of frozen blood samples to Radiobiology lab, Muenster at the cost of Dept. of Radiation Oncology, University Hospital Muenster**).**
- Imaging
  - CT-scan thorax and abdomen
  - abdominal and cervical ultrasound
  - planning CT for radiation
- Endoscopy
  - esophagogastroduodenoscopy (with biopsy)
  - endosonography upper GI-tract (EUS)
  - video capsule endoscopy
  - (ileo)colonoscopy (to evaluate additional disease within GI-tract)
- Quality of life
  - QoL assessment with QLQ-C30 and STO-22

8.1.1 Compulsory examinations in case of <u>suspected involvement</u>

- ENT examination
- Liver biopsy
- Bone scan
- Ileocolonoscopy with biopsies
- Video Capsule Endoscopy
- CT head/neck
- bronchoscopy
- liquor puncture
- MRI
- Bone marrow puncture (cytology, immuncytology, histology, cytogenetics)

All examinations should be performed within 10 days after inclusion in the study. RT should begin at maximum 3 months after study inclusion.

8.1.2 Histologic diagnosis

8.1.2.1 Gastroscopy

Endoscopic procedures are of keen importance for the diagnosis of gastrointestinal lymphoma enabling an exact histologic classification. Therefore, a standardized and quality-controlled approach via „gastric mapping“ (Ruskoné-Fourmestraux 2011) is mandatory in our study including the following procedures:

- 1 biopsy out of antrum and gastric body for urease rapid test
- 10 biopsies out of macroscopical suspicious areas (preservation in formalin and histologic examination)
- 1 biopsy out of any macroscopical unsuspicious quadrant of antrum and gastric body (8 in total)
- 2 biopsies out of gastric fundus
- documentation of endoscopy and the „gastric mapping“ on the documentation form

In case of a suspected gastric lymphoma after first endoscopy, the aforementioned biopsies likely require a second gastroscopy. For participating sites in Germany, it is recommended to send histologic samples to one of the 8 German reference centers of lymphoma pathology (see chapter 16.3 Appendices). Sites outside Germany consult their own routinely addressed pathologists.

8.1.2.2 Endoscopic bowel examination

In case of a suspected bowel involvement of lymphoma beyond the duodenum (e.g. seen as wall thickening on CT scans or during colonoscopy), endoscopic control should be performed by the least invasive way. Therefore, we recommend the use of a video capsule endoscopy to screen for mucosal changes. If a lymphoma involvement is to be proven, a colonoscopy and or double-balloon examination should be performed. In study centers, where a video capsule endoscopy is not available, ileocolonoscopy and double-balloon endoscopy should be employed first.
<u>Importantly, in case of a **gastric lymphoma** prior to treatment the patients must undergo **colonoscopy** to confirm the absence of additional disease within the GI-tract</u>.
If biopsies are taken, the following numbers are recommended:

- 4 biopsies from macroscopical suspicous areas (preservation in formalin and histologic examination)
- 2 biopsies each from terminal ileum/ colon ascendens/ colon transversum/ colon descendens/ sigma/ rectum

In case of a suspected intestinal lymphoma after first endoscopy, the aforementioned biopsies likely require a second gastroscopy. For participating sites in Germany, it is recommended to send histologic samples to one of the 8 German reference centers of lymphoma pathology (see chapter 16.3 Appendices). Sites outside Germany consult their own routinely addressed pathologists.

8.1.2.3 Endosonography

The following parameters have to be documented:

- Horizontal extension
- Longitudinal extension
- Depth infiltration (mucosa, submucosa, muscularis propria, serosa)
- Lymph node involvement

8.1.3 Staging

The modified Ann-Arbor-classification is used for staging:

stage	***involvement***
I	Involvement of a single gastrointestinal organ
I_1	limited to mucosa or submucosa
I_2	extension beyond submucosa
II	Involvement of a GI-organ and regional lymph nodes (LN) and/or extraorgan extension
II_1	Involvement of a GI-organ and regional lymph nodes (II_1) and/or adjacent organs (II_1E) infradiaphragmal
II_2	Involvement of a GI-organ and lymph nodes beyond regional lymph nodes infradiaphragmal (II_2) with a possible localized involvement of another extralymphatic organ (II_2E)
III	Involvement of a GI-organ and lymph node involvement infra- or supradiaphragmal with a possible localized involvement of another extralymphatic organ (IIIE) or spleen (III_S) or both (III_SE)
IV	Diffuse or disseminated (non-GI) involvement with or without lymph-node involvement

Remarks:

- The suffix „E“ is only employed in case of an infiltrative extension („per continuitatem“) in adjacent organs (e.g. stomach→ liver or esophagus or duodenum)
- In the case of simultaneous involvement of stomach and intestinum, no established staging exists
- Perigastric lymph node <1 cm are not considered to be involved in the GI NHL
- B-symptoms: As a weight loss > 10 % is potentially induced by the tumor location, only fever and night sweats are considered to be „B-symptoms

8.2 Intermediate Visits

8.2.1 Intermediate visits 1-4 (IV-1=first day, IV-2=2nd day, IV-3=5th day, IV-4=last day of RT)

The intermediate visit 1 (IV -1) marks the beginning of RT, at the latest the assessment of quality of life with QLQ-C30 and STO-22 is to be performed before the start of RT .

The IV-2, IV-3 and IV-4 visits include blood draw!

At all intermediate visits (IV-1 – IV-4) acute radiogenic reactions must be documented (see Appendix 16.5 Adverse Reactions according to CTCAE).

Specific intermediate visits (IV-1, IV-2, IV-3, IV-4) will take place with IV-4 finishing the RT-treatment including the following aspects:

- Anamnesis
- Clinical examination: ECOG, weight, blood pressure
- **Q**uality **o**f **l**ife assessment with QLQ-C30 and STO-22 **(at IV-4)**
- **Blood draw after (!!) RT fraction (at IV-2/-3/-4):**
    - –Routine: small blood count, LDH, GOT, GPT, alcalic phosphatase, γ-GT, bilirubin, creatinine.
    - –**Research program (analyses at the University of Muenster!):**
      Two 7.5 - 9 ml serum monovettes.
      Centrifugation, freezing and storage see 3.1.3 and Appendix 16.7 (SOP BLOOD SAMPLES for RESEARCH PROGRAM)
      Transmission of frozen blood samples to Radiobiology lab, Muenster at the cost of Dept. of Radiation Oncology, University Hospital Muenster**).**
- Acute radiogenic reactions must be documented (see Appendix 16.5. Adverse Reactions according to CTCAE)

Importantly, all treatments, therapies and taken medication till the end of the study should be documented on the respective clinical file. Any use of simultaneous anti-lymphoma treatment (e.g. chemo-, immunotherapy, steroids) is forbidden. Anyhow, corticosteroid intake for non-malignancies (e.g. asthma, inflammatory diseases) may be permitted up to a dose of 4 mg dexamethason or 20 mg of prednisone per day.

8.3 Follow-up examinations

8.3.1 FU-1

The first follow-up visit after RT takes place 6 weeks after the termination of RT ± 5 days and should include the following examinations:

- Anamnesis
- Clinical examination: ECOG, weight, blood pressure
- Acute radiogenic reactions must be documented (see Appendix 16.5 Adverse Reactions according to CTCAE)

8.3.2 FU-2 – FU-6

The further exams take place quarterly in the first year after treatment (FU-2 – FU-5), afterwards an annual visit is scheduled (FU-6).

FU-2: 3 months after end of RT ± 3 weeks
FU-3: 6 months after end of RT ± 3 weeks
FU-4: 9 months after end of RT ± 3 weeks
FU-5: 12 months (1 year) after end of RT ± 3 weeks
FU-6: 24 months (2 years) after end of RT ± 3 weeks

The FU-2 and FU-3 visits include blood draw!

At all follow-up visits (FU-2 – FU-6) chronic radiogenic reactions must be documented (see Appendix 16.6 Adverse Reactions according to LENT SOMA).

Each follow-up visit consists of the following examinations:
- Anamnesis
- Clinical examination: ECOG, weight, blood pressure
- (at FU-1/-2/-3/-5/-6)
- Quality of life assessment with QLQ-C30 and STO-22 (at FU-1/-2/-3)
- Endoscopy/ Endosonography (+ biopsies) (at FU-2/-3/-5/-6)
- CT-imaging (at FU-3/-5/-6)
- **Blood draw (at FU-2/-3):**
    - –Routine: small blood count, LDH, GOT, GPT, alcalic phosphatase, γ-GT, bilirubin, creatinine.
    - –**Research program (analyses at the University of Muenster!):**
      Two 7.5 - 9 ml serum monovettes.
      Centrifugation, freezing and storage see 3.1.3 and Appendix 16.7 (SOP BLOOD SAMPLES for RESEARCH PROGRAM)
      Transmission of frozen blood samples to Radiobiology lab, Muenster at the cost of Dept. of Radiation Oncology, University Hospital Muenster
- Chronic radiogenic reactions must be documented (see Appendix 16.6 Adverse Reactions according to LENT SOMA)

The FU-6 is the study termination visit and ends the study regularly.

8.4 Follow-up

After study termination, there are no scheduled examinations although the following information should be sent annually to the study management in Muenster:

- **Status**: patient is dead, alive with recurrence, alive without recurrence or lost to follow-up (indicate the day of last contact)
- In **case of dead**, the date and cause of death should be noted.

The study management in Muenster will contact the respective treating oncologist in case that no information on follow-up is provided.

9 Management and reporting of adverse events/adverse reactions

9.1 Definitions

Adverse reactions (AR), acute toxicity: the **Common Terminology Criteria for Adverse Events (CTCAE),** formerly called the Common Tocxicity Criteria, are a set of criteria for the standardized classification of adverse reactions or effects of medical treatment used in cancer therapy. The CTCAE system is a product of the US National Cancer Institute (NCI).

The clinical relevant version 3.0 was released in 2006 (see Appendix 16.5). It uses a range of grades from 1 to 5, specific conditions and symptoms have values or descriptive comment for each level, the general guideline is:

Grade 1	mild
Grade 2	moderate
Grade 3	severe
Grade 4	life-threatening
Grade 5	death

Adverse reactions (AR), chronic toxicity: the **LENT SOMA** (**L**ate **E**ffects on **N**ormal **T**issue, **S**ubjectiv, **O**bjectiv, **M**anagement) score criteria are a set of criteria for the standardized classification of adverse effects of medical treatment used in cancer therapy. The LENT SOMA Tables for the gastrointestinal system with regard to the stomach and the small intestine are:
Grade 1/ 2/ 3/ 4. **S**ubjective, **O**bjective, **M**anagement, **A**nalytic (see Appendix 16.6).

An **Adverse Event (AE)** is defined as an event impairing the patient's health status in comparison to the status before therapy regardless if this event is related to RT or not. Pre-existing medical conditions, planned hospitalizations, study diagnostic testing and procedures as well as an asymptomatic lymphocytosis are not considered as AE. Adverse events categorized as "serious" (SAE) are for e.g. results in death, illness requiring hospitalization, events deemed life-threatening, results in persistent or significant disability/incapacity, a congenital anomaly/birth defect or medically important condition. The grades of adverse events are defined as:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activity living
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activity of daily lifing
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE

9.2 Collection and reporting of AE/AR

Events linked to tumor progression are not considered to be severe AE or AR.

Collection/reporting of **AR**:
Occurrence and grading of AR are to be documented on the forms on acute and chronic toxicity during the follow-up and sent to the study center within 7 days. If the respective AR is not mentioned on the RT-form, number (see Appendices 16.5 for AR-CTCAE and 16.6 for AR-LENT SOMA) and grading should be added by signature. If an AR is not listed in CTC-criteria or the LENT SOMA-criteria, the category "Other" is applied and staged according to grading of AR (s. chapter 9.1).
In case of an AR causing hospitalization, prolongation of a hospitalization, physical handicap, life threatening events or gametopathy, the duration and therapy of AR as well as the possible causal link to lymphoma or therapy are to be documented on the form for acute or chronic AR (AR-CTCAE or AR-LENT SOMA) and sent to the study center within 24 h during RT and within 15 days during follow-up (per fax 0049-251-83-47355). Severe AR are carefully reviewed by the study center in Muenster and evaluated, according to their causal relation to the study treatment.

An accumulation of **grade 3 or grade 4 adverse reactions** according to CTCAE or LENT SOMA, in comparison to the prospective Muenster trials GIT NHL 01/92, GIT NHL 02/96 or DSGL may require a preliminary end of study (see 9.2.3).

Collection/reporting of **AE**:
Occurrence and grading of AE are to be documented on the RT-form during the follow-up and sent to the study center within 7 days. If the respective AE is not mentioned on the RT-form, the symptom with number (see Appendices 16.5 and 16.6 for AR/AE) and grading should be added by signature.
In case of an AE causing hospitalization, prolongation of a hospitalization, physical handicap, life threatening events or gametopathy, the duration and therapy of AE as well as the possible causal link to lymphoma or therapy should be documented as SAE and sent to the study center within 24 h during RT and within 15 days during follow-up (per fax 0049-251-83-47355). SAE are carefully reviewed by the study center in Muenster and evaluated, according to their causal relation to the study treatment.
There is no statutory reporting obligation for serious adverse events SAE in this study.

9.2.1 Relationship of AR/AE to study treatment

The causal relationship between an AE, especially SAE, or an AR and the study treatment will be evaluated by the lead investigators and the study center in Muenster.

Definitely related:	The AE/AR shows a **substantial temporal and causal relationship** to RT making other possibilities unlikely.
Probable:	The **temporal and causal relationship** between RT and the AE/AR is reasonable assumed but alternative explanations or causalities are not definitely ruled out.
Possible:	A temporal sequential relationship between AE/AR and RT is suggested but the **clinical pattern of AE/AR is not typical.**
Unlikely:	The relationship between RT and the occurred AE/AR is improbable and **other medical conditions**, therapies, diseases, medication or a lymphoma progression may better explain the AE/AR.
Not related:	The AE/AR shows no known chronological order or temporal relationship to RT and is **most likely caused by another etiology**.
Not assessable:	The available data does not permit to evaluate the relationship between AE/AR and study treatment.

In any case, the outcome of AE/AR whether causal relationship to treatment exists or not, has to be reported according to the following scheme.

Recovered/ Resolved:	Complete restoration of clinical state before AE/AR
Recovering/ Resolved:	Reduction in intensity of symptoms/signs already occurred suggesting a complete recovery during the further investigation
Not recovered/ Not resolved	Clinical condition of patient remains unchanged or worsened
Recovered resolved with sequel:	Incomplete resolving or resolution of AE/AR with persistent after-effects which should be graded
Fatal:	AE/AR leading to death (grade V toxicity, SAE, s. 9.2.3).
Unknown:	Incomplete or inconsistent information on outcome

9.2.2 Management of AR

All interventions (medication, treatments and therapies) aimed to improve/reduce AR are to be documented according to the following scheme:

None: No actions taken
Medication: Any drug use to counteract AR (also changes in prescribed amount of existent medication).
Other: Any other measures taken, especially operative procedures

The remarks on simultaneous medication during the study period, as indicated under 8.2, have to be considered. Stimulating hematologic agencies as colony stimulating factor or erythropoietin are only allowed to ameliorate the respective cytopenia.

9.2.2.1 Changes in Radiotherapy

Greater changes in the RT-regime define a dropout for the individual patient and are to be reported to the lead investigators or study management within 2 working days:

Dose reduction: Reduction in total/daily dose of RT not indicated in the study (e.g. a reduction from 2 to 1.8 Gy would be possible, a change of dose of at most 10% is possible)
Dose increase: Dose increase beyond the indicated RT dosage of the treatment (a change of dose of at most 10% is possible)
Discontinuation: Pause of RT treatment for one or several days additional to regular pauses (weekend, public holidays) (a pause of RT for at most 4 working days is possible)

Dropout: see 9.2.3.1

Holds and restarts of radiation treatment can be made at the discretion of the treating physician. Any changes in procedure of RT and reasons therefore need to be reported to the lead investigators.

9.2.3 End of study

9.2.3.1 End of study for individual patients

There might by several conditions making it necessary for the patient to be taken out of the study:

- Excessive high grade toxicity (grade III or IV CTCAE)
- Withdrawal of informed consent for study participation of the patient (in that case, the patient is excluded)
- Treating physician’s decision considering the general medical condition of the patient to end study
- Loss of contact to the patient
- Confirmed or suspected pregnancy
- Major violations of the study protocol (e.g. unability to adhere to the study schedule)
- Death of the patient

Each preliminary end of treatment has to be documented and patient is monitored concerning the remission status and overall survival as he/she is not included in the treatment analysis (per protocol).

9.2.3.2 Preliminary end of study

The following reasons may necessitate a preliminary termination of the whole trial

- Excessive number of non-responders or rapid relapses
- Excessive incidence of ≥ III° toxicities CTACE, especially multiple V° toxicities
- New results from other studies or publications, making a continuation of this trial unreasonable or unethical

In the aforementioned cases, the lead investigators inform the Steering Committee of the ILROG, as constituted by international experts in the field of RT in lymphoma diseases, about the issue which has to decide on a study continuation within one month.

9.3 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established to provide the sponsor with recommendations regarding study modification, continuation or termination. (This includes the decision on how to proceed after contact with the Steering Committee of ILROG in case of severe adverse events.)

Procedures governing the convening and execution of the responsibilities of the DMC are specified:

The DMC is a group of radiooncological experts external to the Study Management in Muenster, assessing the progress, safety of data and, if needed critical efficacy endpoints of the study. The DMC may review unhidden study information during the conduct of the study. Based on its review the DMC can submit recommendations regarding study modification, continuation or termination.
A closed DMC meeting should be performed at half-time of the study (i.e. after the first year) or at the discretion of the study investigators. The documentation of a DMC meeting is kept in the study center in Muenster for 10 years.

10 Milestones

10.1 Study Duration

Planned recruitment duration: 1.5 years

Duration of single patient participation: between 6 months - 2 years

Planned overall duration of the study: 2 years

Planned start of data collection (first patient inclusion): September 01, 2019

Last patient inclusion: February 28, 2021

Planned end of data collection: (August 31, 2021). Under the impact of the COVID 19 pandemic the study period will be extended by 6 months until February 28 2022.

Planned final report of study results: (August 2022) February 28 2023.

11 Statistical Considerations

11.1 Methods against bias

Deviating radiation doses or field sizes and differences in expertise of persons executing radiation treatment are potential sources of bias. All patients fulfilling the inclusion and no exclusion criteria and providing informed consent will get the single-arm radiation concept with 20 Gy with clear directives for Investigational project/ Medical procedure. Moreover, the participating sites are limited to university centers and large radiooncological centers, some of them already showed good recruitment in the previous studies, for ensuring a high consistent level of expertise. Because of the low incidence of the disease and the limited trial period a one-sample design is chosen for this study, a randomized trial is biometrically not possible. As there is only one arm no blinding takes place.

11.2 Proposed sample size/Power calculations

The primary endpoint ORR 6 months after the end of RT will be analyzed by a one-sample binomial test. Based on previous studies (Tsang 2003, Teckie 2015) the OR rate of the standard 30 Gy treatment is assumed to be 95%. The same OR rate is assumed for the interventional 20 Gy treatment. To show the non-inferiority of the interventional treatment to a non-inferiority margin of 10% (i.e. show that the ORR is greater than 85%) with 80% power and one-sided significance level 2.5% a number of 79 patients need to be analyzed. It is assumed that 95% of patients assessed for eligibility are assigned to the trial from which another 95% of patients can be analyzed (drop-out rate 5%). That is the needed number of patients to be assigned to the trial is 83 and the necessary number of patients assessed for eligibility is 88.

11.3 Statistical Analysis

The primary efficacy analysis will include all patients to be analyzed and will be performed according to the ITT principle. Primary analysis provides confirmatory statistical evidence. Further analyses will be regarded exploratory (hypothesis generating) and will be interpreted accordingly.
The primary endpoint, the OR rate 6 months after end of treatment, will be tested using one-sample binomial test for the non-inferiority hypothesis. The respective null hypothesis is
H_0: $p \leq p_0 - \delta = 0.95 - 0.1 = 0.85$,
where p is the ORR of the interventional 20Gy treatment, p_0=0.95 is the assumed ORR of the standard 30Gy treatment based on historical data, and δ=0.1 is the non-inferiority margin.
Beyond the ITT analysis of the primary outcome, sensitivity analyses will be performed. In per-protocol analyses only patients without major protocol violations are included.
Statistical analyses of the pre-specified secondary endpoints will be performed using descriptive and inductive statistical methods according to the type of variable.
Additional exploratory analyses will include model-based analyses, subgroup analyses, and safety analyses. In safety analyses all study patients that underwent radiation therapy will be included (safety population).

12 Data Sources and Data Management

12.1 Patient Identification List

All subject data will be collected in a pseudonymized form. Every trial participant can be identified by a unique subject identification code consisting the initial letter of the name of country, a three digit center code, a hyphen and three digit patient numbers. The identification code is assigned by the Study Center Muenster, Germany. A confidential subject identification list, which links the patients' names with the subject identification code, will be stored in the investigator site file locally at each participating site.
Patient numbers at one site are to be used by the radiation oncology and haemato-oncology departments simultaneously.
In case of study termination (either regularly or preliminary) patient name and patient number are kept.

12.2 Source Data

Source data are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the trial. Source data will be documented in various source documents (e.g. hospital records, doctor's report, subjects' diaries or evaluation checklists, x-rays) and then entered into the electronic Case Report Form (eCRF).

Data from patient self-documentation (i.e. EORTC QLQ C30 and STO22) are considered as source data and will be recorded on paper by the patient or a person assisting the patient and subsequentl will be manually entered into the eCRFs by study site personnel.

12.3 Recording of Data /Case Report Form (CRF)

Data will be recorded electronically using an EDC (Electronic Data Capture) system. Only persons authorised to enter data into the eCRF will have access to the EDC system. All users will be trained to use the EDC system and will comply with the instructions in the study-specific user manual. They will have continuous access to the data and reports of subjects at their own study site. The investigator is responsible for ensuring that the study data will be documented correctly, completely and in a timely manner. A study team physician takes on responsibility for the collected data by signing electronically. The electronic signature according to FDA 21 CFR Part 11 is the legally binding equivalent of the study team physician's handwritten signature.

12.4 Data management

For data management, the validated data management system MACRO v4 (Elsevier InferMed) will be used. All entered data will be stored on servers of the University Hospital Muenster. The servers are located in a secure data center and behind a firewall in the network of the University Hospital Muenster. A backup of the data will be saved on a daily basis and all data changes will be recorded in an audit trail.

All data will be checked for plausibility during initial data entry. Missing or non-plausible data are highlighted by the system right at input at the clinical study site and may be corrected immediately.

After completion of data entry and data processing, the database will be locked and the data will be exported for statistical analysis. If required, the investigator will receive a CD-ROM of

the eCRF data for archiving at the clinical study site. Study related documents must be archived for 10 years after the end of treatment.

13 Ethical and Regulatory Requirements

13.1 Ethical approval by institutional review board (University of Muenster)

Patientenschutz | Forschungsfreiheit

ÄRZTEKAMMER WESTFALEN-LIPPE

WWU MÜNSTER

ETHIK KOMMISSION
der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität

Ethik-Kommission Münster · Gartenstraße 210 – 214 · 48147 Münster

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E-Mail: ethik-kommission@aekwl.de
www.ethik-kommission.uni-muenster.de

Ethics Committee Muenster: **2019-023-f-S**, ethical approval July 15, 2019.

13.2 Declaration of Helsinki and Legal Requirements

The study will be conducted in compliance with the declaration of Helsinki (current version, October 2013, Fortaleza), the current legal provisions regarding data protection.

The present study can be launched for each participating study site as soon as a favorable opinion of the respective Ethics committee/IRB has been obtained.

In case of substantial amendments, new applications will be submitted to the relevant Ethics committee(s)/IRB(s).

No deviations from the protocol will be implemented without prior review and approval of the Ethics Committee/ IRB, except where it may be necessary to eliminate and immediate hazard to a patient enrolled on the protocol. In such cases, the deviation will be reported to the Ethics Committee/ IRB as soon as possible.

13.3 Patient Information and Informed Consent

Prior to inclusion into the study, the investigator informs each patient about nature, significance, implications, and risks of the study as well as about the patient's right to withdraw from study participation at any time without any resulting detriment. Patients are handed out the patient information sheet including the informed consent form which are provided for this study. Patient consent in study participation must be given in writing. Before informed consent is requested, patients are left sufficient time for consideration. They are provided the opportunity for clarification of any study issues.

The informed consent form is dated and signed by the patient and by the investigator. The originally signed informed consent form is archived in the investigator site file. A copy of the signed informed consent form (or a second original) is handed over to the patient together with a copy of the patient information sheet.

13.4 Data Protection

This study will be performed in compliance with the applicable data protection laws. Study personnel will handle all patient data in a strictly confidential way.

To prevent the identification of a person to whom study data belong, study data will be pseudonymized by means of the patient identification number (see chapters 6, 12.1). If patient documents (e.g., examination results) are transferred to an institution outside the study site, copies will be used on which the patient's name and initials are obscured and the patient identification number is indicated.

13.5 Financing

An application for funding was submitted to the IZKF Muenster and to the DLH-foundation.

14 Reporting and Publication Policy

14.1 Final report

After completion of the biometric evaluation, the lead investigators prepare a study report. The report includes all trial results, irrespective of whether favorable or not. It is signed by them and the person who is responsible for the evaluation.

Within 12 months after the end of the study, the lead investigators submit a summary of the final report to the Ethics committee/ IRB.

14.2 Publication Policy

The study is registered in the clinical trials database clinicaltrials.gov NCT04097067, which is accessible to the public.
The registration number of the respective organization is XX.

Decisions on authorship are made by the lead investigators under possible counselling with the Steering Committee of ILROG and take into account the conceptual contribution to the study, the participation in the study working groups as well as the number of recruited patients. Manuscripts may only be submitted after consent by all co-authors. Consent for publication may be assumed to be granted if no revisions are claimed by the co-authors 3 weeks after submission of the manuscript draft.

15 References

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National Institutes of Health National Cancer Institute: Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 published: August 9, 2006.; https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf (accessed on December 8, 2018)

- EORTC Quality of Life: validated questionnaires, QLQ-C30 version 3.0, 1995 https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-QLQ-C30-English.pdf (accessed on december 8, 2018)
- EORTC Quality of Life: validated questionnaires, QLQ-STO22 version 1.0, 1999 https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-STO22-English.pdf (accessed on december 8, 2018)

16 Appendices

16.1 Appendix A: List of participating centers:

	Full name of Investigator	City and name of institution
1.	Prof. M.D. Ye-Xiong Li M.D. Shunan Qi	Cancer Hospital, Dept. of Radiation Oncology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 9 Dongdan 3rd Alley, DongDan, Dongcheng Qu, **Beijing** Shi, China, 100006
2.	Prof. Dr. med. Oliver Micke	Franziskus Hospital Bielefeld, Klinik für Strahlentherapie und Radioonkologie, Kiskerstraße 26, 33615 **Bielefeld**
3.	Prof. Dr. med. Martin Stuschke Dr. med. Thomas Gauler	Universitätsklinikum Essen, Klinik für Strahlentherapie, Hufelandstraße 55, 45147 **Essen**
4.	Prof. Dr. med. Hans Christiansen Dr. med. Frank Bruns	Medizinische Hochschule Hannover, Klinik für Strahlentherapie und spezielle Onkologie, Carl-Neuberg-Straße 1, 30625 **Hannover**
5.	Prof. Dr. med. Klaus Herfarth	Universitätsklinikum Heidelberg, RadioOnkologie und Strahlentherapie, Im Neuenheimer Feld 400, 69120 **Heidelberg**
6.	Prof. Dr. med. Jürgen Dunst Frau Kirsten Eilf	Universitätsklinikum Schleswig-Holstein, Klinik für Strahlentherapie, Arnold-Heller-Straße 3, 24105 **Kiel**
7.	Prof. Dr. Simone Marnitz-Schulze Dr. Christian Baues	Uniklinik Köln, Klinik und Poliklinik für Radioonkologie, Cyberknife- und Strahlentherapie, Kerpener Straße 62, 50937 **Köln**
8.	Prof. Dr. med. Rolf-Dieter Kortmann	Universität Leipzig, Klnik für Strahlentherapie und Radioonkologie, Stephanstraße 9a, 04103 **Leipzig**
9.	Prof. Dr. med. Rita Engenhart-Cabillic	Universitätsklinikum Gießen und Marburg GmbH, Standort Marburg, Klinik für Strahlentherapie und Radioonkologie, Baldingerstrasse, 35043 **Marburg**,
10.	Prof. Dr. med. Ursula Nestle	Kliniken Maria Hilf GmbH, Klinik für Strahlentherapie, Viersener Straße 450, 41063 **Mönchengladbach**

11.	Prof. Dr. med. Claus Belka Dr. med. Minglun Li	Klinikum der Universität München (LMU), Klinik für Strahlentherapie, Marchioninistrasse 15, 81377 **München**
12.	Prof. Dr. med. Stephanie E. Combs	Klinikum r. d. Isar d. Technischen Universität München, Klinik für RadioOnkologie und Strahlentherapie, Ismaningerstr. 22, 81675 **München**
13.	Prof. Dr. med. Hans Theodor Eich Dr. med. Gabriele Reinartz	Universitätsklinikum Münster, Klinik für Strahlentherapie und Radioonkologie, Albert-Schweitzer-Campus 1, Gebäude A1, 48149 **Münster**
14.	Prof. M.D. Joachim Yahalom	Memorial Sloan Kettering Cancer Center, Radiation Oncology, 1275 York Ave, **New York**, NY 10065, USA
15.	Prof. M.D. Louis Sandy Constine	University of Rochester, Department of Radiation Oncology, Wilmot Cancer Institute, 601 Elmwood Ave, **Rochester**, NY 14642-0001
16.	Ass. Prof. M.D. Yeoh Kheng-Wei	National Cancer Centre, Radiation Oncology, 11 Hospital Drive, **Singapore** 169610
17.	Prof. M.D. Masahiko Oguchi Ass. Prof. M.D. Senzo Taguchi	The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Dept. Radiation Oncology, 3丁目-8-31 Ariake, Koto, **Tokyo** 135-0063, Japan
18.	Prof. M.D. Umberto Ricardi	University of Torino, Radiation Oncology, Via Giuseppe Verdi, 8, 10124 **Torino** TO, Italien
19.	Prof. Dr. med. Daniel Zips Dr. med. Frank Heinzelmann	Universitätsklinikum Tübingen, Universitätsklinik für Radioonkologie, Hoppe-Seyler-Str. 3, 72076 **Tübingen**
20.	Ass. Prof. M.D. MPH Andrea K. Ng	Dana-Farber Cancer Institute, 450 Brookline Ave, **Boston**, MA 02215, USA
21.	Ass. Prof. M.D. MPH Joanna C. Yang	Department of Radiation Oncology, University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, Box 1708,1600 Divisadero St, H1031, **San Francisco**, CA 94115
22.	Prof. M.D. Richard Tsang, FRCPC	University of Toronto, Radiation Oncology, Princess Margaret Cancer Centre, 610 University Avenue, **Toronto**, ON, M5G 2M9

16.2 Appendix B: GELA criteria:

-CR (complete remission) = **CR or pMRD** (probable minimal residual disease)
-PR (partial remission) = **rRD** (responding residual disease)
-NC (no change)
-PD (progressive disease)

16.3 Appendix C: Reference centers of lymphoma pathology:

Prof. Dr. med. Alfred Feller
Hämatopathologie Lübeck
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Prof. Dr. med. Wolfram Klapper
Universitätsklinikum Schleswig-Holstein (UKSH, Campus Kiel)
Institut für Hämatopathologie und Lymphknotenregister Kiel
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24105 Kiel
Tel.: (+49) 0431 597-3401
Fax: (+49) 0431 597-3462
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Prof. Dr. med. Peter Möller
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Tel.:(+49) 0731 500-56321
Fax: (+49) 0731 500-56384
www.uniklinik-ulm.de/struktur/institute/pathologie.html, peter.möller@uniklinik-ulm.de

Prof. Dr. med. German Ott
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Robert-Bosch-Krankenhaus
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Fax: (+49) 0711 8101-3619
www.rbk.de/standorte/robert-bosch-krankenhaus/abteilungen/pathologie.html

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www.pathodiagnostik.de

16.4 Appendix D: QoL Documentation (validated questionnaires QLQ-C30 version 3.0 and QLQ-STO22 of the EORTC)

(Separate PDF)

16.5 Appendix E (p. 44-62): Adverse Reactions (AR) CTCAE criteria version 3.0 (2006)

Grades
Grade refers to the severity of the AE (adverse event). The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Adverse Reactions (AE) criteria CTCAE version 3.0 (2006) for

BLOOD/BONE MARROW, CONSTITUTIONAL SYMPTOMS, DEATH, DERMATOLOGY/SKIN, ENDOCRINE, GASTROINTESTINAL, HEMORRHAGE/BLEEDING, HEPATOBILIARY/PANCREAS, METABOLIC/LABORATORY, PAIN-SELECT, PULMONARY/UPPER RESPIRATORY, RENAL/GENITOURINARY

16.6 Appendix F (p.63-74): Adverse Reactions (AR) LENT SOMA criteria

for ESOPHAGUS, STOMACH, SMALL INTESTINE/COLON, LUNG, URETER, KIDNEY, LIVER, BONE MARROW, SKIN/SUBCUTANEOUS TISSUE (Archambeau 1995, Cassady 1995, Coia et al. 1995, LENT SOMA for all anatomic sites 1995)

16.7 Appendix G: Standard Operating Procedure (SOP) Blood samples for research program

Standard_Blood samples for Gastric and Duodenal Lymphoma Research Programm_STTH

(within ILROG-Study ISRT 20 Gy in Localized Indolent Gastric or Duodenal Lymphoma)

Aims and scope:

This SOP aims at maintaining constant condition for the cytokine/biologic marker determination minimizing inter-observer variability and thus enabling high-quality data across all participating centers.

Therefore, the following standard applies to all study centers willing to participate in the "Additional Research Program" (see Study protocol 3.1.3 for further information).

Procedure:

Blood draws are intended at 6 consecutive dates (shown in Table 1) for analyzing the cytokines Interleukin (IL)-1ß, IL-4, IL-8 and TNFalpha as well as the proteins Syndecan1, MMP-2 and S100 proteins S100A8 and S100A9.

Visits	BV	IV-1	IV-2	IV-3	IV-4	FU-1	FU-2/3
	Baseline visit	First day of RT treatment	2nd day of RT (**after 4 Gy**)	5th day of RT (**after 10 Gy**)	Last day of RT (**after 20 Gy**)	6 weeks after end of RT ± 5 d	**3 and 6 months** after end of RT ± 3 weeks
Blood draw	X		X	X	X		XX

Table 1.

Blood collection:

- collect 15 - **18 ml** of venous blood by sterile venipuncture using two 7.5 - 9 ml serum monovettes with clotting activator

-for clotting of blood, samples should be stored at room temperature for 20-30 minutes

- **Serum isolation and storage should be performed in a central/biology laboratory** of the clinic:

- the monovettes should be centrifuged for 10 min at 1500 x g

- the supernatant (serum) should be aliqoted by pipetting about 1ml of the serum into separate 2 ml cryotubes or 2ml Eppendorf reaction tubes, so that at least 4 serum aliquots are available from each blood withdrawal (attention: to avoid cellular contamination, release of half a centimeter of serum is indicated and pipette should not put deeper than half a centimeter over pellet into the monovette)

- Aliquots should immediately be stored **at least at -20°C in a freezer**

DANGER: - Repeated freeze-thaw cycles should be avoided and the time from blood collection to freezing of serum should not take longer than 40-60 minutes.

Transfer:

Each participating center stores its serum samples at maximum till the end of patient recruitment.

In the second half of the first year and after the end of recruitment, samples are sent on dry ice to the radiobiology lab in Muenster. Please make sure each sample is labeled with the participant's study ID and date of blood withdrawal. Only correctly labeled samples can be analyzed. Labeling of serum samples in accordance with the **6 visit dates** '**baseline, 4 Gy, 10 Gy, 20 Gy, 3 months, 6 months**':
'Country_center-patient-visit'
->e.g. 'G001-001-baseline' (G=Germany, 001=Muenster, 001=first patient, baseline visit).

For shipment, samples should be put in a fitting small box and placed in a bigger polystyrene box together with about 6kg dry ice. The box should be sealed with adhesive tape.

Please address your samples to:

Prof. Dr. Burkhard Greve

Department of Radiation Oncology – Radiobiology Lab

University Hospital Münster

Robert-Koch-Str. 31
48149 Münster

Germany

In case of questions concerning sample handling and transfer, please do not hesitate to contact us (Prof. Dr. B. Greve: burkhard.greve@ukmuenster.de. Tel.: +49-251-83-52537 or Dr. M. Oertel: Michael.oertel@ukmuenster.de Tel.: +49-251-83-47358)

Material:

+ 7.5 - 9ml serum monovettes with clotting activator

+ pipette (e.g. Pasteur pipette)

+ 2ml cryotubes or 2ml Eppendorf reaction tubes

+ centrifuge

+ freezer

+ dry ice

+ small box

+ polystyrene box

Appendix E: Adverse Reactions (AE) criteria CTCAE version 3.0 (2006)
>> Parameters highlighted in yellow are to be documented in eCRF<<

BLOOD/BONE MARROW

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemoglobin	Hemoglobin	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Leukocytes (total WBC)	Leukocytes	<LLN – 3000/mm3 <LLN – 3.0 x 10^9/L	<3000 – 2000/mm3 <3.0 – 2.0 x 10^9/L	<2000 – 1000/mm3 <2.0 – 1.0 x 10^9/L	<1000/mm3 <1.0 x 10^9/L	Death
Lymphopenia	Lymphopenia	<LLN – 800/mm3 <LLN x 0.8 – 10^9/L	<800 – 500/mm3 <0.8 – 0.5 x 10^9/L	<500 – 200 mm3 <0.5 – 0.2 x 10^9/L	<200/mm3 <0.2 x 10^9/L	Death
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	<LLN – 1500/mm3 <LLN – 1.5 x 10^9/L	<1500 – 1000/mm3 <1.5 – 1.0 x 10^9/L	<1000 – 500/mm3 <1.0 – 0.5 x 10^9/L	<500/mm3 <0.5 x 10^9/L	Death
Platelets	Platelets	<LLN – 75,000/mm3 <LLN – 75.0 x 10^9/L	<75,000 – 50,000/mm3 <75.0 – 50.0 x 10^9/L	<50,000 – 25,000/mm3 <50.0 – 25.0 x 10^9/L	<25,000/mm3 <25.0 x 10^9/L	Death
Blood/Bone Marrow – Other (Specify,)	Blood – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CONSTITUTIONAL SYMPTOMS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fatigue (asthenia, lethargy, malaise)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	Fever	38.0 – 39.0°C (100.4 – 102.2°F)	>39.0 – 40.0°C	>40.0°C (>104.0°F) for ≤24 hrs	>40.0°C	Death

REMARK: The temperature measurements listed are oral or tympanic. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
NAVIGATION NOTE: Hot flashes are graded as Hot flashes/flushes in the ENDOCRINE CATEGORY.						
Insomnia	Insomnia	Occasional difficulty sleeping, not interfering with function	Difficulty sleeping, interfering with function but not interfering with ADL	Frequent difficulty sleeping, interfering with ADL	Disabling	—
REMARK: If pain or other symptoms interfere with sleep, do NOT grade as insomnia. Grade primary event(s) causing insomnia.						
Obesity[2] REMARK: BMI = (weight [kg]) / (height [m])[2]	Obesity	—	BMI 25 – 29.9 kg/m[2]	BMI 30 – 39.99 kg/m[2]	BMI ≥40 kg/m[2]	—
Odor (patient odor)	Patient odor	Mild odor	Pronounced odor	—	—	—

[2] NHLBI Obesity Task Force. "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults," *The Evidence Report,* Obes Res 6:51S- 209S, 1998.

CONSTITUTIONAL SYMPTOMS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Weight gain	Weight gain	5 – <10% of baseline	10 – <20% of baseline	≥20% of baseline	—	—
REMARK: Edema, depending on etiology, is graded in the CARDIAC GENERAL or LYMPHATICS CATEGORIES. ALSO CONSIDER: Ascites (non-malignant); Pleural effusion (non-malignant).						
Weight loss	Weight loss	5 to <10% from baseline; intervention not indicated	10 – <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	—	—

DEATH

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Death not associated with CTCAE term – *Select*:	Death not associated with CTCAE term – *Select*	—		—		Death

– Death NOS
– Disease progression NOS
– Multi-organ failure
– Sudden death

REMARK: Grade 5 is the only appropriate grade. 'Death not associated with CTCAE term – *Select'* is to be used where a death:
1. Cannot be attributed to a CTCAE term associated with Grade 5.
2. Cannot be reported within any CATEGORY using a CTCAE 'Other (Specify,)'.

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Atrophy, skin	Atrophy, skin	Detectable	Marked	—	—	—
Atrophy, subcutaneous fat	Atrophy, subcutaneous fat	Detectable	Marked	—	—	—
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue).						
Dry skin	Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—
Hair loss/alopecia (scalp or body)	Alopecia	Thinning or patchy	Complete	—	—	—
Hyperpigmentation	Hyperpigmentation	Slight or localized	Marked or generalized	—	—	—
Hypopigmentation	Hypopigmentation	Slight or localized	Marked or generalized	—	—	—
Induration/fibrosis (skin and subcutaneous tissue)	Induration	Increased density on palpation	Moderate impairment of function not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; very marked density, retraction or fixation	—	—
ALSO CONSIDER: Fibrosis-cosmesis; Fibrosis-deep connective tissue.						

DERMATOLOGY/SKIN

	Grade

Adverse Event	Short Name	1	2	3	4	5
Rash/desquamation	Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
REMARK: Rash/desquamation may be used for GVHD.						
Rash: dermatitis associated with radiation – *Select*: – Chemoradiation – Radiation	Dermatitis – *Select*	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death

ENDOCRINE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Endocrine – Other (Specify)	Endocrine – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Abdominal pain or cramping is graded as Pain – *Select* in the PAIN CATEGORY.						
Anorexia	Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALSO CONSIDER: Weight loss.						

Ascites (non-malignant)	Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
REMARK: Ascites (non-malignant) refers to documented non-malignant ascites or unknown etiology, but unlikely malignant, and includes chylous ascites.						
Colitis	Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
ALSO CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (e.g., hemodynamic collapse)	Death
ALSO CONSIDER: Diarrhea; Hypotension; Vomiting.						

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea. ALSO CONSIDER: Dehydration; Hypotension.						

Distension/bloating, abdominal	Distension	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic, interfering with GI function	—	—

ALSO CONSIDER: Ascites (non-malignant); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dysphagia (difficulty swallowing)	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death

REMARK: Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilation is graded as Stricture/stenosis (including anastomotic), GI – *Select*.
ALSO CONSIDER: Dehydration; Esophagitis.

Enteritis (inflammation of the small bowel)	Enteritis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death

ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).

Esophagitis	Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death

REMARK: Esophagitis includes reflux esophagitis.
ALSO CONSIDER: Dysphagia (difficulty swallowing).

GASTROINTESTINAL

		Grade				

Adverse Event	Short Name	1	2	3	4	5
Fistula, GI – *Select*: – Abdomen NOS – Duodenum – Esophagus – Ileum – Jejunum – Stomach	Fistula, GI – *Select*	Asymptomatic, radiographic findings only		Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs		Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer is graded as Fistula, GI – esophagus.						
Flatulence	Flatulence	Mild	Moderate	—	—	—
Gastritis (including bile reflux gastritis)	Gastritis	Asymptomatic radiographic or endoscopic findings only	Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs	Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., gastrectomy)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Ulcer, GI – *Select*.						
NAVIGATION NOTE: Head and neck soft tissue necrosis is graded as Soft tissue necrosis – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Heartburn/dyspepsia	Heartburn	Mild	Moderate	Severe	—	—

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Ileus	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥24 hrs	Life-threatening consequences	Death

REMARK: Ileus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying).
ALSO CONSIDER: Constipation; Nausea; Obstruction, GI – *Select*; Vomiting.

Leak (including anastomotic), GI – *Select*: – Esophagus – Leak NOS – Small bowel – Stomach	Leak, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interfering with GI function; invasive or endoscopic intervention indicated	Life-threatening consequences	Death

REMARK: Leak (including anasomotic), GI – *Select* is to be used for clinical signs/symptoms or radiographic confirmation of anastomotic or conduit leak (e.g., biliary, esophageal, intestinal, pancreatic, pharyngeal, rectal), but without development of fistula.

Malabsorption	Malabsorption	—	Altered diet; oral therapies indicated (e.g., enzymes, medications, dietary supplements)	Inability to aliment adequately via GI tract (i.e., TPN indicated)	Life-threatening consequences	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stomatitis (clinical exam) – *Select*: – Esophagus – Small bowel – Stomach	Mucositis (clinical exam) – *Select*	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death

REMARK: Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.

Mucositis/stomatitis (functional/symptomatic) – *Select*: – Esophagus – Large bowel – Larynx – Small bowel – Stomach	Mucositis (functional/ symptomatic) – *Select*	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Anorexia; Vomiting.						

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Necrosis, GI – *Select*: – Colon/cecum/appendix – Duodenum – Ileum – Jejunum – Stomach	Necrosis, GI – *Select*	—		Inability to aliment adequately by GI tract (e.g., requiring enteral or parenteral nutrition); interventional radiology, endoscopic, or operative intervention indicated		Death
ALSO CONSIDER: Visceral arterial ischemia (non-myocardial).						

Obstruction, GI – *Select*: – Colon – Duodenum – Esophagus – Ileum – Jejunum – Stomach	Obstruction, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death

NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.

NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Perforation, GI – *Select*: – Esophagus – Gallbladder – Ileum – Jejunum – Small bowel NOS – Stomach	Perforation, GI – *Select*	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated <24 hrs	IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences	Death
Prolapse of stoma, GI	Prolapse of stoma, GI	Asymptomatic	Extraordinary local care or maintenance; minor revision indicated	Dysfunctional stoma; major revision indicated	Life-threatening consequences	Death

REMARK: Other stoma complications may be graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Obstruction, GI – *Select;* Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select*.

NAVIGATION NOTE: Rectal or perirectal pain (proctalgia) is graded as Pain – *Select* in the PAIN CATEGORY.

NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.

GASTROINTESTINAL

		Grade				

Adverse Event	Short Name	1	2	3	4	5
Stricture/stenosis (including anastomotic), GI – *Select*: – Biliary tree – Duodenum – Ileum – Jejunum – Small bowel NOS – Stomach	Stricture, GI – *Select*	Asymptomatic radiographic findings only		Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated		Death

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GI – *Select*: – Abdomen NOS – Biliary tree – Colon – Duodenum – Esophagus – Liver – Lower GI NOS – Oral cavity – Stomach – Upper GI NOS	Hemorrhage, GI – *Select*	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death

REMARK: Transfusion implies pRBC.
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).

HEPATOBILIARY/PANCREAS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**

NAVIGATION NOTE: Biliary tree damage is graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Necrosis, GI – *Select*; Obstruction, GI – *Select*; Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Cholecystitis	Cholecystitis	Asymptomatic, radiographic findings only	Symptomatic, medical intervention indicated	Interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*.						
Liver dysfunction/failure (clinical)	Liver dysfunction	—	Jaundice	Asterixis	Encephalopathy or coma	Death
REMARK: Jaundice is not an AE, but occurs when the liver is not working properly or when a bile duct is blocked. It is graded as a result of liver dysfunction/failure or elevated bilirubin. ALSO CONSIDER: Bilirubin (hyperbilirubinemia).						
Hepatobiliary/Pancreas – Other (Specify,)	Hepatobiliary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Albumin, serum-low (hypoalbuminemia)	Hypoalbuminemia	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	—	Death
Alkaline phosphatase	Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
ALT, SGPT (serum glutamic pyruvic transaminase)	ALT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
AST, SGOT (serum glutamic oxaloacetic transaminase)	AST	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Bilirubin (hyperbilirubinemia)	Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	—
REMARK: Jaundice is not an AE, but may be a manifestation of liver dysfunction/failure or elevated bilirubin. If jaundice is associated with elevated bilirubin, grade bilirubin.						

[4]Crit Rev Clin Lab Sci 1984;21(1):51-97

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Creatinine	Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death
REMARK: Adjust to age-appropriate levels for pediatric patients. ALSO CONSIDER: Glomerular filtration rate.						
GGT (γ-Glutamyl transpeptidase)	GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Glomerular filtration rate	GFR	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Creatinine.						
Hemoglobinuria	Hemoglobinuria	Present	—	—	—	Death

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Proteinuria	Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome	Death

PAIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pain – *Select*: '*Select*' AEs appear at the end of the CATEGORY.	Pain – *Select*	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—
Pain – Other (Specify,)	Pain – Other (Specify)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—

PAIN – *SELECT*

HEPATOBILIARY/PANCREAS
– Gallbladder - Liver
-- Liver
RENAL/GENITOURINARY
– Kidney
-- Bladder

GASTROINTESTINAL
– Abdomen NOS
– Esophagus
– Peritoneum
– Stomach

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Atelectasis	Atelectasis	Asymptomatic	Symptomatic (e.g., dyspnea, cough), medical intervention indicated (e.g., bronchoscopic suctioning, chest physiotherapy, suctioning)	Operative (e.g., stent, laser) intervention indicated	Life-threatening respiratory compromise	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Obstruction/stenosis of airway – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Bronchospasm, wheezing	Bronchospasm	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Dyspnea (shortness of breath).						
Cough	Cough	Symptomatic, non- narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	—	—

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dyspnea (shortness of breath)	Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death
ALSO CONSIDER: Hypoxia; Neuropathy: motor; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
FEV_1	FEV_1	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted	Death
Fistula, pulmonary/upper respiratory – *Select*: – Bronchus – Lung – Trachea	Fistula, pulmonary – *Select*	Asymptomatic, radiographic findings only	Symptomatic, tube thoracostomy or medical management indicated; associated with altered respiratory function but not interfering with ADL	Symptomatic and associated with altered respiratory function interfering with ADL; or endoscopic (e.g., stent) or primary closure by operative intervention indicated	Life-threatening consequences; operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have arisen. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer should be graded as Fistula, GI – esophagus in the GASTROINTESTINAL CATEGORY.						
NAVIGATION NOTE: Hemoptysis is graded as Hemorrhage, pulmonary/upper respiratory – *Select* in the HEMORRHAGE/BLEEDING CATEGORY.						
Hypoxia	Hypoxia	—	Decreased O_2 saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased O_2 saturation at rest; continuous oxygen indicated	Life-threatening; intubation or ventilation indicated	Death

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**

Obstruction/stenosis of airway – *Select*: – Bronchus – Trachea	Airway obstruction – *Select*	Asymptomatic obstruction or stenosis on exam, endoscopy, or radiograph	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; tracheotomy or intubation indicated	Death
Pleural effusion (non-malignant)	Pleural effusion	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g., causing hemodynamic instability or ventilatory support indicated)	Death
ALSO CONSIDER: Atelectasis; Cough; Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pneumonitis/pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Pneumothorax	Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic; intervention indicated (e.g., hospitalization for observation, tube placement without sclerosis)	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated	Death

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**

Pulmonary fibrosis (radiographic changes)	Pulmonary fibrosis	Minimal radiographic findings (or patchy or bi-basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 – <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50 – <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death
REMARK: Fibrosis is usually a "late effect" seen >3 months after radiation or combined modality therapy (including surgery). It is thought to represent scar/fibrotic lung tissue. It may be difficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy. ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select.*						
NAVIGATION NOTE: Recurrent laryngeal nerve dysfunction is graded as Laryngeal nerve dysfunction in the NEUROLOGY CATEGORY.						
Vital capacity	Vital capacity	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
Pulmonary/Upper Respiratory – Other (Specify,)	Pulmonary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fistula, GU – *Select*: – Kidney – Ureter	Fistula, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; noninvasive intervention indicated	Symptomatic interfering with ADL; invasive intervention indicated	Life-threatening consequences; operative intervention requiring partial or full organ resection; permanent urinary diversion	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated.						
Leak (including anastomotic), GU – *Select*: – Kidney – Ureter	Leak, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic, interfering with GU function; invasive or endoscopic intervention indicated	Life-threatening	Death

REMARK: Leak (including anastomotic), GU – *Select* refers to clinical signs and symptoms or radiographic confirmation of anastomotic leak but without development of fistula.

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Perforation, GU – *Select*: – Fallopian tube – Kidney – Ovary – Prostate – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Perforation, GU – *Select*	Asymptomatic radiographic findings only	Symptomatic, associated with altered renal/GU function	Symptomatic, operative intervention indicated	Life-threatening consequences or organ failure; operative intervention requiring organ resection indicated	Death
Renal failure	Renal failure	—	—	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death

ALSO CONSIDER: Glomerular filtration rate.

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	Urinary electrolyte wasting	Asymptomatic, intervention not indicated	Mild, reversible and manageable with replacement	Irreversible, requiring continued replacement	—	—
ALSO CONSIDER: Acidosis (metabolic or respiratory); Bicarbonate, serum-low; Calcium, serum-low (hypocalcemia); Phosphate, serum-low (hypophosphatemia).						
Urinary frequency/urgency	Urinary frequency	Increase in frequency or nocturia up to 2 x normal; enuresis	Increase >2 x normal but <hourly	≥1 x/hr; urgency; catheter indicated	—	—

Urine color change	Urine color change	Present	—	—	—	—
REMARK: Urine color refers to change that is not related to other dietary or physiologic cause (e.g., bilirubin, concentrated urine, and hematuria).						
Renal/Genitourinary – Other (Specify,)	Renal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

Appendix F: Adverse Reactions (AR) LENT SOMA criteria for ESOPHAGUS, STOMACH, SMALL INTESTINE/COLON, LUNG, URETER, KIDNEY, LIVER, BONE MARROW, SKIN/SUBCUTANEOUS TISSUE
(Archambeau 1995, Cassady 1995, Coia et al. 1995, LENT SOMA for all anatomic sites 1995)

ESOPHAGUS

	GRADE 1	GRADE 2	GRADE 3	GRADE 4	SCORING
Subjective					**Instructions**
Dysphagia	Difficulty eating solid foods	Difficulty eating soft foods	Can take liquids only	Totally unable to swallow	**Score the 11 SOM parameters with 1-4**
Pain	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating	
Objective					**(Score = 0 if there are no toxicities)**
Weight loss from time of treatment	≥5% - 10%	> 10% -20%	> 20% -30%	>30%	
Stricture	> 2/3 normal diameter with dilatation	> 1/3 - 2/3 normal diameter with dilatation	≤ 1/3 normal diameter	Complete obstruction	
Ulceration	Superficial ≤ 1 cm²	Superficial > 1 cm²	Deep ulcer	Perforation, fistulae	**Total the score and** Divide by 11
Bleeding (melena or hematemesis)	Occult	Occasional, normal hemoglobin	Intermittent, 10% - 20% decrease in hemoglobin	Persistent, > 20% decrease in hemoglobin	
Anemia		Fatigue	Exhaustion		
Management					**LENT Score:**
Dysphagia / Stricture	Diet modification or antacids	Diet modification and occasional dilatation	Temporary NG tube or regular dilatation	Parenteral feeding, prosthesis, gastrostomy or permanent NG tube	
Weight loss	Diet modification	Nutritional supplements	Tube feeding	Surgical bypass, PEG	
Pain / Ulceration	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention	
Bleeding	Iron therapy	Occasional transfusion	Frequent transfusions	Surgical intervention	

Analytic		
Barium esophagram	Assessment of esophageal lumen, stricture, dilatation	Y/N Date:
Endoscopy	Assessment of esophageal lumen, mucosal integrity, ulceration	Y/N Date:
CT	Assessment of esophageal wall thickness, lumen, stricture, dilatation	Y/N Date:
MRI	Assessment of esophageal wall thickness, lumen, stricture, dilatation	Y/N Date:
Ultrasonography	Assessment of esophageal wall thickness, lumen, stricture, dilatation	Y/N Date:
Mobility esophagram	Assessment of motility of bolus and peristalsis	Y/N Date:
Electromyogram	Assessment of motility of bolus and peristalsis	Y/N Date:

STOMACH

	GRADE 1	GRADE 2	GRADE 3	GRADE 4	SCORING
Subjective					**Instructions** **Score the 13 SOM parameters with 1-4**
Epigastric distress	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating	
Emesis	Occasional	Intermittent	Persistent	Refractory	
Pain	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating	
Objective					**(Score = 0 if there are no toxicities)**
Hematemesis	Occasional≥ 5%- 10%	Intermittent	Persistent	Refractory	
Weight loss from time of treatment	Occult / Occasional, normal hemoglobin	> 10%-20%	>20% -30%	>30%	
Melena	Superficial, ≤ 1cm² > 2/3 normal diameter	Intermittent, < 10% decrease in hemoglobin	Persistent, 10% - 20% decrease in hemoglobin	Refractory or frank blood, > 20% decrease in hemoglobin	**Total the score and divide by 13**

Ulceration Stricture (Antro-pyloric region)		Superficial, > 1 cm² 1/3 - 2/3 normal diameter	Deep ulcer < 1/3 normal diameter	Perforation, fistulae Complete obstruction	
Management					**LENT Score:**
Epigastric distress / Emesis	Diet modification, antacids	Intermittent prescription medication	Persistent medical management	Surgical intervention	
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention	
Bleeding	Iron therapy	Occasional transfusion	Frequent transfusions	Embolization, coagulation or surgical intervention	
Ulceration			Medical intervention	Surgical intervention	
Stricture			Medical intervention	Surgical intervention	
Analytic					
Barium radiography	Assessment of lumen and peristalsis				Y/N Date:
Endoscopy	Assessment of lumen and mucosal surface				Y/N Date:
CT	Assessment of wall thickness, sinus and fistula fonnation				Y/N Date:
MR!	Assessment of wall thickness, sinus and fistula formation				Y/N Date:

SMALL INTESTINE / COLON

	GRADE 1	GRADE 2	GRADE 3	GRADE 4	SCORING
Subjective					**Instructions** **Score the 13 SOM**
Stool frequency	2-4per day	5-8per day	> 8 per day	Refractory diarrhea	
Stool consistency	Bulky	Loose	Mucous, dark, watery		**parameters**
Pain	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory / Rebound	**with 1-4**

Constipation	3 - 4 per week	On!, 2 per week	Only 1 per week	No stool in 10 days	
Objective Melena	Occult / Occasional	Intermittent & tolerable, normal hemoglobin	Persistent, 10% - 20% decrease in hemoglobin	Refractory or frank blood, >20% decrease in hemoglobin	**(Score = 0 if there are no toxicities)**
Weight loss from time of treatment	≥ 5%-10%	> 10% -20%	>20% -30%	>30%	
Stricture	> 2/3 normal diameter with dilatation	1/3 - 2/3 normal diameter with dilatation	< 1/3 normal diameter	Complete obstruction	**Total the score and divide by 13**
Ulceration	Superficial < 1 cm^2	Superficial > 1 cm^2	Deep ulcer	Perforation, fistulae	
Management Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention	
Stool consistency / frequency	Diet modification	Regular use of non- narcotic antidiarrheal	Continuous use of narcotic antidiarrheal		**LENT Score:**
Bleeding	Iron therapy	Occasional transfusion	Frequent transfusions	Surgical intervention	
Stricture	Occasional diet adaptation	Diet adaptation required	Medical intervention, NG suction	Surgical intervention	
Ulceration			Medical intervention	Surgical intervention	
Analytic CT	Assessment of wall thickness, sinus and fistula formation				Y/N Date:
MRI	Assessment of wall thickness, sinus and fistula formation				Y/N Date:
Absorption studies	Assessment of protein and fat absorption and metabolic balance				Y/N Date:
Barium radiograph	Assessment of lumen and peristalsis				Y/N Date:

Lung

	GRADE I	GRADE 2	GRADE 3	GRADE 4	SCORING
Subjective					**Instructions**
Cough	Occasional	Intermittent	Persistent	Refractory	**Score the 8 SOM**
Dyspnea	Breathless on intense exertion	Breathless on mild exertion	Breathless at rest, limits all activities	Prevents any physical activity	**Parameters with 1-4**
Chest pain/discomfort	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating	
Objective					**(Score = 0 if there are no toxicities)**
Pulmonary fibrosis	Radiological abnormality	Patchy dense abnormalities on radiograph	Dense confluent radiographic changes limited to radiation field	Dense fibrosis, severe scarring & major retraction of normal lung	
Lung function	10% - 25% reduction of respiration volume and/or diffusion capacity	> 25% - 50% reduction of respiration volume and/or diffusion capacity	> 50% - 75% reduction of respiration volume and/or diffusion capacity	> 75% reduction of respiration volume and/or diffusion capacity	**Total the score and divide by 8**
Management					
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention	**LENT Score**
Cough		Non-narcotic	Narcotic, intermittent corticosteroids	Respirator, continuous corticosteroids	
Dyspnea		Occasional O_2	Continuous O_2		
Analytic					
PFT	Decrease to >75% -90% of preTx value	Decrease to >50% - 75% of preTx value	Decrease to >25%-50% of preTx value	Decrease to ≤ 25% of preTx value	*Y/N* Date:

DLCO % O_2/CO_2 saturation	Decrease to >75% -90% of preTx value > 70% O_2, ≤ 50% $C0_2$	Decrease to >50% - 75% of preTx value > 60% 0_2, ≤ 60% $C0_2$	Decrease to >25%-50% of preTx value > 50% 0_2, ≤ 70% CO_2	Decrease to ≤ 25% of preTx value ≤50% 0_2, >70% $C0_2$	Y/N Date: Y/N Date:
CT/ MRI Perfusion scan Lung lavage	Assessment of lung volume and zones of fibrosis Assessment of pulmonary blood flow and alveolar filling Assessment of cells and cytokines				Y/N Date: Y/N Date: Y/N Date:

Ureter

	GRADE 1	GRADE 2	GRADE 3	GRADE 4	**SCORING**
Subjective Pain	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating	**Instructions** **Score the 5 SOM parameters with 1-4**
Objective Obstruction Renal function	Ureteral narrowing without hydronephrosis 1+ proteinuria	Ureteral narrowing with hydronephrosis 2+ proteinuria	Unilateral obstruction 4+ proteinuria	Bilateral obstruction	**(Score = 0 if there are no toxicities)**

Management Pain Obstruction	Occasional non-narcotic	Regular non-narcotic	Regular narcotic Unilateral stent or nephrostomy	Surgical intervention Bilateral nephrostomy or diversion	**LENT Score:**
Analytic Intravenous pyelography	Assessment of ureter integrity				Y/N Date:

Kidney

	GRADE 1	GRADE 2	GRADE 3	GRADE 4	**SCORING**
Subjective Symptoms			Fatigue, headache	Obtundation, oliguria, edema	**Instructions**
Objective Blood pressure		systolic ≤ 20 over normal diastolic ≤ 10 over normal	systolic > 20 over normal diastolic > 10 over normal	Malignant hypertension	**Score the 7 SOM parameters with 1-4**
Hematuria	Microscopic	Intermittent macroscopic	Persistent macroscopic	Refractory	
Edema	None or transient	Pedal; 2+ - 3+	Pedal 4+, edema of lower leg(s)	Uremic coma, anasarca	**Score = 0 if there are no toxicities}**
Specific gravity		Urine SpG decreased			

Management Blood pressure/ Renal failure Hematwia	Diet Iron therapy	Antihypertension medication Occasional transfusion or single cauterization	Dialysis, unilateral nephrectomy Persistent transfusion or coagulation	Permanent dialysis or Renal transplant ·surgical intervention	**Total the scores and divide by 7**
Analytic Proteinuria Creatinine clearance Creatinine B2 Microglob.	< 3 gm/l 5% - 10% decrease 1.25 x normal - 2.5 x normal	3 gmfl - 10 gmfl > 10% - 30% decrease > 2.5 x normal - 5 x normal	> 10 gm/l > 30% - 60% decrease >5xnonnal-10x normal > 2 x normal - 4 x normal	Nephrotic syndrome > 60% decrease > 10 x normal > 4 x normal	Y/N Date: Y/N Date: Y/N Date: Y/N Date:
Glomerular filtration rate Renal scanning	Quantification of filtration rate Assessment of renal size and radioisotope clearance				Y/N Date: Y/N Date:

LIVER

	GRADE 1	GRADE 2	GRADE 3	GRADE 4	**SCORING**
Subjective Pain RUQ	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating	**Instructions**
Objective Abdominal findings	Hepatomegaly	Soft ascites	Tense ascites		

Edema	Occasional leg edema	Intermittent leg edema	Anasarca responsive to diuretics	Anasarca unresponsive to diuretics	**Score the 9 SOM parameters with 1-4 (Score = 0 if there are no toxicities)**
Weight gain		≤ 5%	>5%- 10%	>10%	
Alertness		Change in attentiveness and sleep pattern	Confusion	Coma	
Bleeding			Correctable	Unresponsive	
Management					
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Continuous narcotic	**Total the scores and divide by 9**
Abdominal findings		Intermittent diuretics	Permanent diuretics		
Bleeding		Iron therapy	Occasional transfusion of fresh frozen plasma	Frequent transfusions	**LENT Score**
Analytic					
AST/ALT /Alk phos	< 2.5 x normal	2.5 - 5.0 x normal	> 5.0 - 20.0 x normal	> 20.0 x normal	Y/N Date:
Bilirubin	< 1.5 x normal	1.5 - 5.0 x normal	> 5.0 - 10.0 x normal	> 10.0 x normal	Y/N Date:
PT/ PTT	< 1.25 x normal	1.25 - 1.5 x normal	> 1.50 - 2.0 x normal	> 2.0 x normal	Y/N Date:
Serum alb (gm/dl)[3]	> 3.0	> 2.5 - 3.0	> 2.0- 2.5	≤ 2.0	Y/N Date:
Platelets (1,OOO)	> 75.0	> 50.0- 75.0	·> 25.0- 50.0	≤ 25.0	Y/N Date:

BONE MARROW

	GRADE 1	GRADE 2	GRADE 3	GRADE 4	**SCORING**

Subjective Anemia symptoms Leukopenia symptoms Thrombocytopenia symptoms		Fatigue	Exhaustion Fever Easy bruisability	Spontaneous bleeding	**Instructions** **Score the 9 SOM parameters with 1-4**
Objective Anemia Leukopenia Thrombocytopenia	Abnormal aspirate / biopsy	Abnormal Hgb / Hct < 10/<30 Abnormal WBC < 2000 Platelets >20K – l00K	Pallor Infection Platelets >5K - 20 K, petechia	Tachypnea Sepsis Platelets < 5K, hemorrhage	**(Score = 0 if there are no toxicitivies)** **Total the scores and divide by 9**
Management Anemia Leukopenia Thrombocytopenia			Occasional use of red blood products Antibiotics / cytokines Platelets / red blood cells	Frequent use of red blood products Bone marrow transplant	**LENT Score:**
Analytic Assays Chimerism, Clonality	Assessment of bone marrow reserves with: Hematopoietic progenitor cell assays in common use (CFU-GM, BFU-R, CFU-GEMM, CFU-blast. etcJ) Stroma! cell assays (CRU-F, support of long-term bone marrow cultures) Growth factor production Primitive stem cell assays (HPP-CRL, CFU-Dexter, LTC-IC, somatic mutation analysis / DWA analysis) In setting of bone marrow transplant (Studies of mixed (donor/host) chimerism, studies of clonality (donor vs host)) Future consideration: challenge with growth factors to assay stem cell reserve				Y/N Date: Y/N Date: Y/N Date: Y/N Date: Y/N Date:

SKIN / SUBCUTANEOUS TISSUE

	GRADE 1	GRADE 2	GRADE 3	GRADE 4	SCORING
Subjective Scaliness/Roughness Sensation	Present / asymptomatic Hypersensitivity, pruritus	Symptomatic Intermittent pain	Require constant attention Persistent pain	Debilitating dysfunction	**SCORING Instructions Score the 14 SOM parameters with 1-4**
Objective Edema Alopecia (scalp) Pigmentation change Ulcer / Necrosis Telangiectasia Fibrosis / Scar Atrophy / Contraction (depression)	Present / asymptomatic Thinning Transitory, slight Epidermal only Minor Present / asymptomatic Present / asymptomatic	Symptomatic Patchy permanent Permanent, marked Dermal Moderate <50% Symptomatic Symptomatic / < 10%	Secondary dysfunction Complete, permanent Subcutaneous Gross ≥ 50% Secondary dysfunction Secondary dysfunction / 10%-30%	Total dysfunction Bone exposed Total dysfunction Total dysfunction / > 30%	**(Score = 0 if there are no toxicities)** **Total the score and divide by 14**
Management Dryness Sensation Ulcer Edema Fibrosis / Scar		Intermittent medical intervention	Medical intervention Continuous medical intervention Medical intervention Medical intervention Medical intervention	Surgical intervention/ Amputation -- Surgical intervention/ amputation Surgical intervention/ amputation -	**LENT Score:**

Analytic Color photographs	Assessment of changes in appearance	Y/N Date: