PROTOCOL IGR 2006/1202

Phase III study comparing post-operative conformal radiotherapy to no post-operative radiotherapy in patients with completely resected non-small cell lung cancer and mediastinal N2 Involvement.

Abbreviated title of the trial: **Lung ART**
Participating groups:
IGR, IFCT, LARS-G (Lung Adjuvant Radiotherapy Spanish Group),

With the support of INCa (French National Cancer Institute)

Version 8.0 of 10/11/2010

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APPROVAL AND SIGNATURES OF PROTOCOL LUNG ART

"Phase III study comparing post-operative conformal radiotherapy to no post-operative radiotherapy in patients with completely resected non-small cell lung cancer and mediastinal N2 involvement."

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1 SYNOPSIS

A) CLINICAL TRIAL IDENTIFICATION	
PROTOCOL NUMBER : IGR 2006/1202 - IFCT0503 **VERSION AND DATE : VERSION** 8.0 OF NOVEMBER 10TH, 2010	
TRIAL FULL TITLE : Phase III study comparing post-operative conformal radiotherapy to no post-operative radiotherapy in patients with completely resected non-small cell lung cancer and mediastinal N2 involvement.	
ABBREVIATED TITLE OF THE TRIAL : Lung ART (Lung Adjuvant Radiotherapy Trial)	
COORDINATING INVESTIGATOR : **Cécile Le Péchoux, MD** Radiotherapy Department, Institut Gustave Roussy Phone : +33.1.42.11.47.57 Fax : +33.1.42.11.52.53 e-mail : cecile.lepechoux@igr.fr	
NUMBER OF INVESTIGATIONAL SITES PLANNED : 50 sites in France, Netherlands, Belgium, Spain, United Kingdom, Poland, Switzerland	**NUMBER OF PATIENTS :** 700 patients

B) SPONSOR IDENTIFICATION
SPONSOR'S NAME : Institut de cancérologie Gustave Roussy (IGR)
CONTACT PERSON : Gilles VASSAL Adress : Direction de la Recherche Clinique et Translationnelle (DRCT) 114, rue Edouard Vaillant 94805 VILLEJUIF cedex
C) GENERAL INFORMATION ON THE TRIAL

MEDICAL CONDITION :

Patients with completely resected non-small cell lung cancer (NSCLC), histologically or cytologically proven N2 nodal involvement

STUDY DESIGN :

International, multicentre, randomised, phase III trial

OBJECTIVES :

MAIN :

Improvement of disease-free survival (DFS) by conformal thoracic radiotherapy compared to no radiotherapy

SECONDARY :

- Impact of thoracic radiotherapy on toxicity and in particular cardiac and pulmonary toxicity (with identification of plasmatic predictive factors of toxicity),
- Local control,
- Patterns of recurrence,
- Overall survival (OS),
- Second cancers,
- Prognostic factors and predictive factors of treatment effect on DFS and Overall Survival.
- Cost for each year of life without recurrence gained (exclusively in French participating centres).

INCLUSION CRITERIA :

1) Histological evidence of non-small cell lung cancer (NSCLC),
2) Complete resection by lobectomy, bilobectomy or pneumonectomy (i.e patients with positive margins or extra-capsular extension in a node removed separately in case of sampling not to be included)
3) Mediastinal lymph node exploration (lymph node sampling or systematic dissection of lymph nodes at levels 2, 4 and 7 in case of upper/middle right-sided lung cancer; 4, 7, 8 and 9 in case of lower right-sided lung cancer; 5, 6 and 7 in case of upper left –sided lung cancer; 7, 8 and 9 in case of lower left-sided lung cancer is recommended)

4) Pathologically or cytologically documented N2 mediastinal nodal involvement, at the time of surgery if no preoperative chemotherapy or before preoperative chemotherapy, according to the criteria of the joint AJCC and UICC classification, clinical N2 patients without cytological or histological documentation of mediastinal node involvement before preoperative chemotherapy can be included in the study if and only if, they have histologically confirmed N2 disease at the time of surgery.
5) Prior chemotherapy is allowed (pre-operative or post-operative adjuvant chemotherapy, or both),
6) Patient aged ≥18 years,
7) Good Performance status (WHO ≤ 1)
8) Adequate pulmonary function with post-operative FEV1 after surgery > 1 l or over 35% theoretical value, $PO_2 \geq 70$ mmHg, $PCO_2 < 45$ mmHg,
9) Signed informed consent form.

EXCLUSION CRITERIA :

1) Documented metastases, (except for ipsilateral nodule(s) in a different lobe after pneumonectomy or bi-lobectomy).
2) Major pleural or pericardial effusion,
3) Synchronous contra-lateral lung cancer,
4) Clinical progression during post-operative chemotherapy,
5) Previous chest radiotherapy
6) Intention of concomitant chemotherapy during radiotherapy
7) Weight loss in the previous 6 months before surgery ≥ 10%
8) Evidence of severe or uncontrolled systemic disease as judged by the investigator
9) Recent (< 6 months) severe cardiac disease (arrhythmia, congestive heart failure, infarction, pace-maker) or pulmonary disease
10) Current or past history of neoplasm other than non-small cell lung cancer diagnosed within the last 5 years, except :
    - basal cell carcinoma of the skin,
    - *in situ* carcinoma of the cervix

    A patient diagnosed for another neoplasm 5 years ago or more, treated and considered as cured may be included in the study if all the other criteria are respected.
11) Pregnancy or breast feeding or inadequate contraceptive measures during treatment,
12) Patients who, for family, social, geographic or psychological reasons, cannot be adequately followed up and/or are incapable of undergoing regular controls,
13) Patient deprived of freedom or under guardianship.

EVALUATION CRITERIA

Primary endpoint

Disease-free survival (DFS)

Secondary endpoint

- Assessment of treatment of acute and late toxicity (with identification of predictive factors of toxicity),
- Local control,
- Patterns of recurrence,
- Overall survival (OS),
- Second cancers,
- Prognostic and predictive factors on DFS and OS
- Cost for each year of life without recurrence gained (exclusively in French participating centres)

TREATMENT SCHEDULE :

All eligible patients will be randomised between

- Thoracic adjuvant conformal radiotherapy at the dose of 54 Gy/27 to 30 fractions
- No thoracic adjuvant radiotherapy

Concomitant chemotherapy is not allowed

Pre-operative, post-operative adjuvant chemotherapy or both are allowed.

Timing of randomisation/surgery and chemotherapy (if any):

- In case of no post-operative CT, randomisation will be performed as soon as possible after histological results of complete surgery. Randomisation should take place **within 6 weeks after surgery**.
- In case of post-operative CT, randomisation should be performed as soon as possible

after the last administration of CT (**within 3 weeks**) and no later than 6 months after surgery.

Timing of radiotherapy :

In patients allocated to RT arm, thoracic radiotherapy should start :

- in case of no post-operative CT, no sooner than 4 weeks after surgery *(and no later than 8 weeks after surgery*) **or**
- in case of post-operative CT, no sooner than 2 weeks after the last administration of chemotherapy *(and no later than 6 weeks after the last administration of chemotherapy)*

and, at the latest, within 3 weeks after randomisation

DOSE MODIFICATIONS :

Not applicable

DURATION OF TREATMENT :

6 weeks for patients receiving conformal radiotherapy

D) STATISTICAL CONSIDERATIONS

SAMPLE SIZE :

700 patients will allow to show a 10% difference in terms of 3-year disease-free survival (bilateral test, power = 80%, alpha=5%, analysis with a median follow-up of 3 years).

STATISTICAL ANALYSIS :

Cox analysis stratified on the factors used for randomisation : Centre, Administration of CT (pre-operative CT alone vs. post-operative CT vs. none), Number of mediastinal lymph nodes involved (0 vs. 1 vs. 2+), Histology (SCC vs. other), Use of pre-treatment PET-scan (Yes vs. no).

E) TRIAL DURATION

INCLUSION PERIOD : 3 to 5 years

TREATMENT PERIOD : 6 weeks for radiotherapy arm

POST TREATMENT PERIOD : up to 10 years

DURATION OF THE TRIAL : up to 10 years

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2 FLOW CHART

	Before surgery	Before randomisation	Treatment						Follow-up								
Weeks/Months			**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**M3**	**M6**	**M12**	**M18**	**M24**	**M30**	**M36**	**M48**	**M60**
Informed consent		x															
Inclusion/Exclusion criteria		x															
Randomisation		x															
TREATMENT																	
Control arm																	
PORT arm			x	x	x	x	x	x									
CLINICAL ASSESSMENT*																	
Clinical examination		x							x	x	x	x	x	x	x	x	x
Toxicity assessment (CTCAE v3.0)		x							x	x	x		x		x	x	x
ADDITIONAL TESTS*																	
Thoracic CT scan §	x	x°								x	x	x	x	x	x	x	x
Abdominal CT scan		x**															
Brain CT scan or MRI		x**															
Pre-operative pulmonary functions	x																
Post-operative FEV1 and DLCO, §		x									x		x		x	x	x
Cardiac ultrasound (within 2 months before surgery) §		x**									x		x		x	x	x
PET Scan (not mandatory)	x																
LABORATORY TESTS*																	
Blood count	x																
Blood sample for translational research		x															

* for all patients ** if not done before the surgery § as indicated in the Follow-up, (but cardiac ultrasound optional for some centers) and in case of grade 3 or higher cardio-pulmonary toxicity
°if performed more than 4 months before randomisation some exams performed before surgery could be used for this protocol

3 RATIONALE OF THE TRIAL

3.1 INTRODUCTION

Over one million people are diagnosed with lung cancer every year throughout the world [Parkin et al, 2001]. About 80% of them have non-small cell lung cancer (NSCLC) which includes adenocarcinoma, squamous cell and large cell carcinoma. Considering all stages together, the 5-year survival rate in NSCLC does not exceed 14% [Rankin et al, 1986]. Most long-term survivors are patients having had a complete surgical resection of their tumour. The latter, considered as the best treatment option, is only achievable in about 30 % of the patients. Even in this highly selected group of patients, there is still a high risk of both local and distant failure. Adjuvant treatments such as chemotherapy (CT) and radiotherapy (RT) have therefore been evaluated in order to improve their prognosis. Whereas individual trials comparing surgery alone to surgery + adjuvant CT could not achieve any significant difference, the meta-analysis published in 1995 showed a modest survival benefit of 5% in completely resected patients having received post-operative cisplatin based adjuvant CT compared to patients without CT [Non-Small Cell Lung Cancer Collaborative Group, 1995]. The benefit of adjuvant chemotherapy has been recently confirmed in 2 meta-analyses and several trials including the IALT with more than 1800 stage I, II and III randomised patients (IALT 2004, Kato 2004, Hamada 2004, Hotta et al, 2004, Strauss et al, 2004, Sedrakyan A, 2004; Winton et al, 2004). The range of the benefit observed with CT varies between 4 % and 15% absolute improvement in the 5-year survival. These results will certainly have a significant impact on the therapeutic approach of such a frequent cancer. Thus, most clinicians will now consider adjuvant chemotherapy as standard treatment in patients with completely resected lung cancer. A new meta-analysis is planned that will take into consideration all recent trials listed before, trials that have not yet been published and recent negative trials [Scagliotti et al, JNCI 2003]. However, even after a complete surgical resection and adjuvant chemotherapy, 20 % to 40 % of the patients still have a local tumour failure as shown on tables 1 and 2. In view of the high proportion of the patients still suffering from local tumour recurrence after a complete resection and adjuvant chemotherapy, a new interest in post-operative radiotherapy (PORT) occurred. However, PORT has been for years a very controversial issue and still is.

The PORT Meta-analysis Trialists Group analysed individual patient data from 2128 patients from nine randomised trials that compared postoperative radiotherapy with surgery alone by intention to treat [PORT Meta-analysis Trialists Group, 1998]. The PORT trials are described in Tables 3 and 4. The median follow-up was 3.9 years for surviving patients. The results of the PORT meta-analysis indicated that postoperative radiotherapy had a significant detrimental effect on survival. There were 707 deaths among 1056 patients assigned to the postoperative

radiotherapy arm versus 661 deaths among 1072 patients included in the surgery alone arm. This represented a 21% relative increase in the risk of death or to an absolute decrease of 7% at 2 years, reducing the overall survival from 55 to 48% (mortality hazard ratio, 1.21; 95% confidence interval [CI], 1.08—1.34; p = 0.001). Subset analyses suggested that PORT could be deleterious in terms of overall survival, predominantly, among patients who had a complete resection and no mediastinal involvement (either pN0 or pN1). However they could observe a 24% relative reduction of local recurrence rate (all stages together), so that the question of post-operative radiotherapy in pN2 who have a high local recurrence rate remained valid and could warrant further research. This meta-analysis has been criticized because radiotherapy techniques used were considered suboptimal, resulting in higher morbidity and mortality rates in the PORT arm than in more recent studies. It should be stressed that seven of the nine trials included patients treated with Cobalt-60 equipment, which is now known to increase morbidity [Philips et al, 1993]. It seems important to evaluate modern post-operative radiotherapy as the number of patients with nodal involvement is increasing because of better surgery and the recent positive results of adjuvant chemotherapy.

3.2 Positioning the issue of PORT in patients with mediastinal nodal involvement

Five-year survival rate of patients with mediastinal nodal involvement who have had a complete resection of NSCLC (pN2) varies around 20% in large surgical series [Mountain et al, 1997; Naruke et al, 1997]. There remains controversy on the prognostic value of several common clinical factors in NSCLC patients with resected N2-disease, and their relative importance varies across studies: age, sex, histology, type of nodal involvement, number of mediastinal nodes involved (1 or more), absence of hilar node involvement, extra-capsular extension [Vansteenkiste 1998, André 2001]. Several biological factors have also been reported such as K-ras mutations, overexpression of p21 and p185neu, absence of BCL2 overexpression, or factors that are pro-angiogenic or may act on the extra-cellular matrix (metalloproteases, cathepsine B), expression of CD44; their respective prognostic value varies also in the different studies [Sekido et al, 2005]. The importance of mediastinal node involvement seems however the best and most consensual prognostic factor. In the largest retrospective study that evaluated survival among 702 resected patients with pN2 disease according to the importance of nodal involvement, a 5-year survival rate of 34% was observed in case of microscopically involvement of a single mediastinal node (single mN2) whereas it went down to 11% in case of multiple nodes with microscopically invasion. The survival rate was lower in case of «clinical N2» involvement of a single node (8%) or several nodes (3%) [André et al, JCO 2001]. In all these patients, the risk of metastatic dissemination is high.

These patients may benefit from adjuvant chemotherapy given post-operatively (as discussed in the previous section) or pre-operatively. Several retrospective studies have indeed suggested a

benefit in terms of survival in favour of pre-operative chemotherapy for patients with mediastinal nodal involvement [André et al, 2001; Martini et al, 1993]. Two randomized small studies, controversial because of their size, confirmed these results, but a larger trial could not confirm these results for the sub-group of N2 patients [Rosell et al, 1994; Roth et al, 1994; Depierre et al, 2002]. Even if it is not evidence-based medicine, several clinicians treat patients with N2 involvement with pre-operative chemotherapy.

In this group of patients, local control is also an important issue. In several prospective studies, the local control is poor among patients with hilar and/or mediastinal involvement so that the reported local failure rate is 41% (pN2 patients only) [MRC working party 1996], 33% in Feng study [Feng et al, 2000], 41% in an older LCSG study [Lung Cancer Study Group 1986]. A retrospective joint study from Japan, evaluated the risk of local failure among pN2 patients, at 39% [Ichinose et al, 2001].

3.3 Post-operative radiotherapy (PORT); local control and toxicity issues

3.3.1 Efficacy of post-operative radiotherapy

The risk of local recurrence is reduced by PORT (25 to 35%) as shown in several retrospective studies listed on Table 1. In most of these studies, there was a historical comparison with patients who had no PORT, so these figures should be interpreted with caution. Since the sixties, several randomized studies have also been undertaken to evaluate the effect of PORT not only on local control but also on survival rates. In most studies, the total dose varied between 40 and 60 Gy, whereas the fraction size ranged from 1.8 to 2.6 Gy, 4 to 5 fractions per week. The techniques used were also quite different from one trial to the other. However most of the trials used at first 2 parallel anterior-posterior opposed fields, to treat the following volume including the 2 supra-clavicular regions, the whole mediastinum and the homo-lateral hilar region up to the dose of 36 to 42 Gy. A boost to a more limited region was delivered with oblique opposed fields, or with anterior-posterior reduced fields with a spinal block. Many of these trials used sub-optimal techniques leading to poor local control and eventually increased toxicity [DiBiase et al, 2000]. There was a significant underdosage in the nodal area at risk, especially in trials recommending the spinal block technique. Furthermore, in most trials included in the meta-analysis, there was no CT scan based planning. Presently, more and more patients have conformal radiotherapy based on CT planning, contributing to reduced toxicity and possibly better local control [Armstrong et al, 2000, Graham et al, 2001]. Some trials have indeed described an over added toxicity in the PORT arm compared to the control arm [Dautzenberg, 1999; PORT meta-analysis, 1998]. This toxicity will be detailed in the next

chapter. The most recent randomized trials are listed in table 2. In the study of Dautzenberg and al, the risk of local recurrence was reduced by 15% with PORT (NS), if one considers the whole population of patients included: pN0, pN1 and pN2, but this risk was reduced by 29% considering only the 190 pN2 patients [Dautzenberg et al, 1999]. In the MRC study, the local recurrence rate among pN2 patients in the control arm was 41% and decreased to 26% among patients who had PORT [Stephens et al, 1996]. In the retrospective study of Ichinose, on 406 patients with pN2 nodal involvement, the local recurrence rate among the 332 evaluated patients was 39.2%, most of these reoccurrences being located in the mediastinum [Ichinose et al, 2001]. Unfortunately, most studies do not give any details on the site of recurrence, and they do not give any detail on the mediastinal exploration : how many nodes were explored and which of them were involved; did sampling or mediastinal dissection was used during the initial surgery. It would certainly be important in such a study to know the site of recurrence in relation to the characteristics of the tumour, the type of mediastinal surgery, as well as the modalities of PORT. In the randomized study recently published by Keller and al, which included patients with stage II and III, comparing PORT to PORT with concomitant chemotherapy, there was a significant difference ($p<0.05$) between the recurrence rate of patients having had a mediastinal dissection (50%) and those who had mediastinal sampling (60%) [Keller, ATS 2000]. In this study, the percentage of locoregional recurrences within the radiotherapy field was around 13% and therefore smaller than those reported in the literature [Keller NEJM 2000].

Table 1: Retrospective studies on PORT

Study	Stage	N patients	Dose Gy	Local Recurrence (%)	Overall survival (%)	Follow-up method
Astudillo	IIIA	60	_	20%	28%	3 years actuarial
		86	45-50	13%	20%	
Green	I-IIIA	94	_	NR	16%	5 years crude
		125	50 - 60	NR	31%	
Choi	IIIA	55		31%	8 %	5 years actuarial
		93	40 - 56	14%	43%	
Chung	I-IIIA	68	_	32%	28%	3 years crude
		50	46	10%	40%	
Patterson	T3N0-2	22	_	27%	30%	5 years actuarial
		13	20-50	0	56%	
Kirsch	IIIA	20	_	NR	0%	5 years crude
		110	50 - 60	NR	26%	
Sawyer	IIIA	136	_	60%	22%	4 years actuarial
		88	45-66	17%	43%	

Table 2: Results of certain randomized studies

Study	Stage	N pts	Total dose / *Fraction size*	LRR (%)	p	5-year SR (%)	P in favour
Van Houtte	T1-3N0	104	_	10.9%	NS	43%	<0.05 Surgery
		98	60/*2* Gy	1.2%		24%	
LCSG	II-III SCC	120	_	41%	0.001	40%	NS
		110	50.4/*1.8*	3%		40%	
GETCB Dautzenberg	I-II-III	355	_	28%	NS	43%	0.002 Surgery
		373	60/*2 to 2.5*	22%		30%	
Mayer¤	I-II-III	72	_	20%*	<0.01	20.4%	NS
		83	50-56/*2*	7%*		29.7%	
Trodella¤	T-2N0	53	_	23%	0.019	58%	0.048 PORT
		51	50.4/*1.8*	2.2%		67%	
Feng	II-III	182		33.2%	0.01	40.5%	NS
		183	60/2	12.7%		42.9%	

- LRR: Local recurrence Rate
- * Cumulative rate of local recurrences
- ¤ These studies were not included in the meta-analysis
- NS non significant

Table 3: Trials included in the PORT meta-analysis

Study	Inclusion	N patients	Total dose (Gy)	Dose/fraction (Gy)
Belgium Van Houtte	1966-1977	202	60	2
LCSG	1978-1985	230	50	1.8 - 2
Lille-Lafitte	1985-1991	163	45 - 60	NR
MRC-Stephens	1986-1993	308	40	2.6
Slovenia-Debevec	1988-1992	74	30	2.5 - 3
GETCB-86 Dautzenberg	1986-1994	189	60	2 - 2.5
GETCB-88 Dautzenberg	1988-1994	539	60	2 - 2.5
CAMS -Wang	1981-1995	317	60	2
EORTC	1986-1990	106	56	2

Table 4: Results of PORT meta-analysis

	2-year survival	p	2-year disease-free survival	p
Surgery	55%	0.001	50%	0.018
Surgery+PORT	48%		46%	

3.3.2 Toxicity reported in post-operative radiotherapy trials

The excess of toxicity (mostly cardiac and pulmonary) and non-cancer related deaths observed in the post-operative radiotherapy arm of the trials included in the meta-analysis can probably be explained by excessive volumes of radiation, old radiation techniques, too large doses and fraction sizes. As described on table 3, we can observe these trials are quite old so that, radiation oncologists had no CT-scan to help delineate the volume of irradiation. Several of these trials used Cobalt and we know that cobalt machine provide an excess of cardiac toxicity compared to linear accelerators [Philipps 1993]. Unfortunately, the authors of the meta-analysis could not collect data on toxicity or causes of intercurrent deaths in the different studies. Among the late cardiac complications that are described after mediastinal radiotherapy, there are

pericarditis, coronary disease, myocardiopathy and valvular abnormalities. They have been described in patients who are long-term survivors to such irradiation, i.e. Hodgkin's disease, breast cancer, and seminoma patients [Adams et al, 2003; Stewart et al, 1995; Zagars et al, 2004; Rutqvist et al, 1992]. This toxicity is linked to the total dose that has been administered, the fraction size, the irradiated volume, the technique of irradiation, as well as comorbidities (tobacco use, overweight). Several authors have underlined the importance of the radiation technique to decrease this risk (Stewart et al, 1995; Overgaard et al, 2000; Machtay 2001; Philipps 1993). Pulmonary complications such as pneumonitis and lung fibrosis can also be observed, but they occur earlier, they are dose and volume dependant. They are mostly related to the percentage of normal lung parenchyma irradiated, the total dose administered as well as pre-existing lung disease [Bentzen et al, 2000]. The administration of certain radiosensitizing drugs may increase this risk.

A new randomized study should take into consideration all we know about toxicity. Conformational radiotherapy should be proposed to all operated patients as their mediastinal location and anatomy may vary after surgery, especially pneumonectomy, in order to decrease the morbidity [Philips et al, 1993; Machtay et al, 2001, von Lieven et al, 2001]. The volume irradiated comprising the two supra-clavicular regions, the whole mediastinum, the homo-lateral hilar region is also considered too large now and contributing to the excess of toxicity observed. The fraction size should be 1.8 or 2 Gy. In the largest published randomized trial, Dautzenberg could determine that the use of fraction sizes larger than 2 Gy was at high risk of late toxicity [Dautzenberg et al, 1999]. A retrospective study published on a selected patients population focused on toxicity issues, showing that PORT could be administered safely if patients were treated with more modern treatment techniques, more limited volume of irradiation, daily fraction sizes $\leq$ 2 Gy, and total dose $\leq$ 54 Gy [Machtay et al, 2001]. The ECOG came to the same conclusions, and reported recently on the 4-year actuarial rate of death from intercurrent disease (DID) for patients treated with PORT within the E3590 trial which was 12,9%. This rate is not significantly different from the 10,1% expected rate of DID observed in a matched control population for age and gender and corrected for smoking status [Wakelee et al, 2005]. The median time to death from intercurrent disease was about 110 months.

3.3.3 Importance of the PET-scan in the evaluation of loco-regional disease

The evaluation of loco-regional disease rests mainly on the thoracic scan with iodine injection. This remains of major importance for diagnosis with the fibroscopy in order to classify the tumour. The advantage of the PET-scan as compared to CT-scan has recently been shown for mediastinal involvement. The sensibility and specificity are 61% and 79% for the CT-scan as compared to 85% and 90% for the PET-scan [Gould 2003]. Therefore, it is an important

diagnostic tool, but it is not easily available in all regions. For the patients initially evaluated with a PET-scan, information will be required as to its results concerning mediastinal involvement compared to médiastinal surgical exploration.

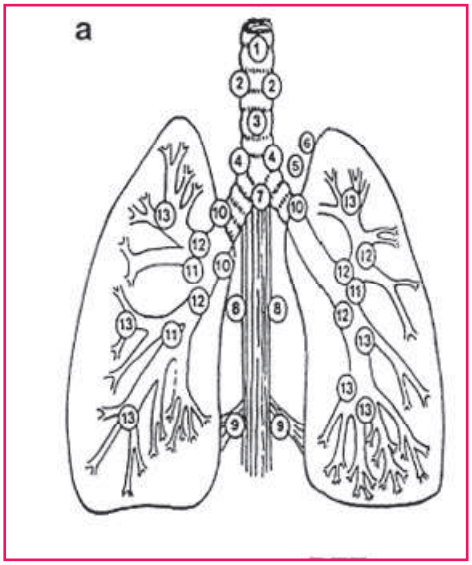
3.3.4 Modalities of conformational mediastinal post-operative radiotherapy

Even if we lack publications giving details on the modalities of local recurrence after surgery, patients recur mostly in the mediastinum, the hilar region and sometimes in the supra-clavicular region [DiBiase SJ, 2000; Ichinose et al, 2001]. However, we do not know precisely where the recurrence occurs. If we consider combined chemotherapy and radiotherapy series without surgery, the initially involved nodes are at higher risk of recurrence so that more and more publications report results where patients have no irradiation of the uninvolved nodes [Senan S et al, 2001; Rosenzweig et al, 2000]. The absence of elective nodal irradiation contributes largely to reduce field sizes.

In order to optimize the modalities of conformational radiotherapy in the post-operative setting, it is important to remember what surgical series have taught us about the risk of nodal failure according to the tumour site [Watanabe et al, 1990].

Table 5: Risk of mediastinal node involvement according to tumour site [Watanabe 1990]

Mediastinal lymph node areas	N°	Tumour site			
		RUL	RML+RLL	LUL	LLL
Upper mediastinum	1	9%	3%	0%	0%
Paratracheal N	2	40%	31%	3%	0%
Pretracheal, retro-tracheal N Or ant mediastinum	3	73%	47%	29%	0%
Tracheobronch	4	36%	28%	17%	13%
Sub-aortic	5	-	-	71%	13%
Para-aortic	6	-	-	43%	25%
Sub-carenal	7	36%	69%	20%	38%
Para-esophageal	8	9%	11%	3%	50%
Pulm ligament	9	2%	6%	6%	13%



RUL Right Upper Lobe LUL Left Upper Lobe
RML Right Medial Lobe LLL Left Lower Lobe
RLL Right Lower Lobe

Thus, if one considers a series of surgical patients with pN2 nodal disease, the risk for lymph node involvement is respectively 48% around the trachea and 41% in the sub-carenal region. Consequently, paratracheal nodes, sub-carenal nodes as well as the homo-lateral hilar region should be systematically included in the irradiation volume. Because of the particular lymphatic path, especially for left-sided tumours, contra-lateral para-tracheal nodes should also be treated [Kiricuta, 1994]. Most authors agree that in this setting, contra-lateral hilar nodes and supra-clavicular nodes should not be included in the treatment volume, as the risk of involvement is low [Kiricuta et al, 1994; Emami et al, 1997, Watanabe et al, 1990].

In this study, will be recorded all lymph node stages explored, as well as the involved nodes. In the PORT treatment arm, the irradiation volume will take into consideration the situation of the tumoral lymph nodes. As said before, homolateral hilar region, the bilateral paratracheal nodes, the sub-carenal nodes as well as the lymph node stations involved will systematically be included in the radiation treatment volume. The immediate superior lymph node station to the upper mediastinal station involved will be included in the planning treatment volume (PTV) as well as immediate inferior lymph node station to the lower involved mediastinal station [Emami 1997]. The radiation therapy recommendations will be detailed on chapter 8.2.

3.4 Where do we stand with PORT in 2005 and implications for the new trial

Considering the toxicity issues that have been developed in the past chapter, is important to recall that in breast cancer, post-mastectomy radiotherapy considered as deleterious for years has recently been rehabilitated after publication of two large randomized studies using more modern radiotherapy techniques [Ragaz et al NEJM 1997, Overgaard et al NEJM 1997]. They both showed a clear benefit in favour post-operative radiotherapy not only in terms of disease-free-survival but also in overall survival.

At present, based on level 1 evidence, patients who have had a complete resection of the primary tumour with mediastinal lymph node dissection showing no mediastinal involvement (pN0 and pN1) should not have PORT. However, based on the meta-analysis, the issue of PORT is not as clear among pN2 patients and warrants further studies with more modern techniques [Arriagada et al, 2003]. The question of PORT remains also among patients who have histologically proven N2 disease before pre-operative chemotherapy, whatever their response is: persistent mediastinal involvement or mediastinal down staging (from N2 histologically proven to pN0 or pN1). There is no randomized study on this issue.

Indication of PORT is currently debated for each individual patient. Some clinicians never consider PORT for pN2 patients, others consider it a standard in pN2 patients, and others restrict their indications of PORT among patients with multiple N2 nodal involvement or in case of extra-capsular extension. Sawyer and al have tried in a study of 224 N2 patients, to divide

them into 3 different sub-groups according their respective risk of failure : high risk (in case of multiple distant mediastinal nodes involved), intermediate (in case of involvement of inferior nodes or superior nodes with eventually invasion of hilar nodes) and low risk (if there is no hilar node involvement) [Sawyer et al, 1997]. However, as with any retrospective study, one should be cautious with the results, very much in favour of PORT, and this delineates the importance of a new randomized study comparing PORT to no PORT in such a frequent cancer as NSCLC, as stressed in most recent articles on PORT in N2 disease. However, in order to avoid the errors of previous studies, it is very important to describe well the modalities of surgery (most particularly the lymph node exploration) as well as the radiotherapy modalities in terms of volume, fields and dose prescription that will be defined and verified by a quality control committee. Conformational radiotherapy should be mandatory. The irradiation volume should take into account the data of thoracic CT scan and the eventual PET scan data before surgery, as well as the description of mediastinal exploration and histopathological results. Sites of recurrence should well be described in this new randomized trial. Such a study would result into an optimization of standard care, as our knowledge of the modalities of local and regional recurrences is poor.

3.5 Hypothesis of the trial

As disease-free survival among completely resected patients with N2 mediastinal node involvement is about 30% at 3 years, with a risk of local recurrence of about 30% at 3 years, we hypothesize that these results could be improved with conformational post-operative radiotherapy. Therefore, we set up a randomized study comparing conformational PORT given at the dose of 54 Gy/27 to 30 fractions to no PORT.

4 OBJECTIVE OF THE TRIAL

The objective of this randomized trial would be to study disease-free survival (DFS) in a population with completely resected non-small cell lung cancer, with homolateral lymph node mediastinal involvement histologically or cytologically proven, who will randomly be assigned to receive conformational PORT or not to receive PORT. The included patients may have had chemotherapy or not. DFS will be evaluated with a median follow-up of 3 years following the randomisation.

Immediate toxicity occurring during the course of radiotherapy or within 90 days following it, will be evaluated with CTCAE v3 scale. Late toxicity will be searched for and evaluated with the CTCAE v3.0 scale. Toxicity will also be searched for in the control group as some “toxicity” related to smoking for example or any other may occur in this group Translational research will be associated, and it will be performed in both groups also (cf appendix).

Local control, patterns of failure, overall survival will be compared in the two groups. Prognostic and predictive factors of radiation therapy effect on Disease free survival and overall survival will be studied. Cost for each year of life without recurrence gained will be evaluated in the French centres in both groups.

5 METHODOLOGY

Phase III multi-institutional international trial comparing after randomisation mediastinal PORT (54 Gy/27 to 30 fractions/6 weeks) to no PORT, with possible individual direct benefit to the patient.

6 SELECTION OF PATIENTS

6.1 Inclusion criteria

1. Histological evidence of non-small cell lung cancer (NSCLC),
2. Complete resection by lobectomy, bilobectomy or pneumonectomy (i.e. patients with positive margins or extra-capsular extension in a node removed separately in case of sampling not to be included)
3. Mediastinal lymph node exploration (lymph node sampling or systematic dissection of lymph nodes at levels 2, 4, and 7, in case of upper/middle right-sided lung cancer; 4, 7, 8 and 9 in case of lower right sided lung cancer; 5, 6 and 7 in case of upper left-sided lung cancer; 7, 8 and 9 in case of lower left-sided lung cancer is recommended).
4. Pathologically or cytologically documented N2 mediastinal nodal involvement, at the time of surgery if no preoperative chemotherapy or before preoperative chemotherapy. according to the criteria of the joint AJCC and UICC classification. Clinical N2 patients without cytological or histological documentation of mediastinal node involvement before preoperative chemotherapy can be included in the study if, and only if, they have histologically confirmed N2 disease at the time of surgery
5. Prior chemotherapy is allowed (pre-operative or post-operative adjuvant chemotherapy, or both),
6. Patient aged ≥18 years,
7. Good Performance status (WHO ≤ 1),
8. Adequate pulmonary function with post-operative FEV1 after surgery > 1 l or over 35% theoretical value, $PO_2 \geq 70$ mmHg, $PCO_2 < 45$ mmHg,
9. Information given to patient and signed informed consent form.

6.2 Exclusion criteria

1. Documented metastases, (except for ipsilateral nodule(s) in a different lobe after pneumonectomy or bi-lobectomy),
2. Major pleural or pericardial effusion,
3. Synchronous contra-lateral lung cancer,
4. Clinical progression during post-operative chemotherapy,
5. Previous chest radiotherapy
6. Intention of concomitant chemotherapy during radiotherapy
7. Weight loss in the previous 6 months before surgery ≥ 10%
8. Evidence of severe or uncontrolled systemic disease as judged by the investigator,
9. Recent (< 6 months) severe cardiac disease (arrhythmia, congestive heart failure, infarction, pace-maker) or pulmonary disease
10. Past or current history of neoplasm other than non-small cell lung cancer, diagnosed within the last 5 years, except :
    - basal cell carcinoma of the skin,
    - in situ carcinoma of the cervix,
    A.patient diagnosed for another neoplasm 5 years ago or more, treated and considered as cured may be included in the study if all the other criteria are respected.
11. Pregnancy or breast feeding or inadequate contraceptive measures during treatment,
12. Patients who, for family, social, geographic or psychological reasons, cannot be adequately followed up and/or are incapable of undergoing regular controls,
13. Patient deprived of freedom or under guardianship.

6.3 Informations requested before randomisation

- Clinical data : weight, size, performance status, Tobacco consumption (past use, current status)
- Biological values (pre-operative evaluation)
- Radiological evaluation to prove there is no metastatic extension :
- Thoracic and abdominal CT scan, and if possible pre-treatment PET-scan, if the thoracic CT scan has been performed more than 4 months before randomization, another one should be performed.
- Brain CT-scan or MRI
- If abdominal or brain CT-scan have not been performed before surgery, they should be performed before radiotherapy
- Measurement of pre-operative pulmonary functions
- Pre-operative cardiac ultrasound (within 2 months before surgery)

- Surgical report
- Histological report corresponding to surgery (lung tumour and mediastinal and nodal histopathology)
- Measurement of Post-operative pulmonary functions (FEV1 or Forced Expiratory Volume in one second, and DLCO or Diffusion Capacity)
- Post-operative cardiac ultra-sound (if not performed before surgery) is mandatory for the centres that follow the yearly cardiac ultra-sound program
- Pre-randomisation toxicities according to CTCAE v3

7 RANDOMISATION

Following information will be requested before randomisation:

- Name of institution and name of physician responsible
- Initials of the patient's name and file number
- Gender
- Date of birth
- Performance status (WHO) before randomisation
- Date of surgery
- PET scan before any treatment (Yes/No) and date
- pTNM stage
- Number of lymph node stations involved
- Histology (squamous cell carcinoma, adenocarcinoma, large cell lung carcinoma, mixed, other)
- Chemotherapy or other adjuvant treatment (neoadjuvant/adjuvant/both/none)

If yes : - Date of last administration of post-operative CT, if any

- Whether the patient will participate to the biological study (blood sample, tumour block)

Eligible patients, being informed and having signed the consent form will be randomized through internet or fax.

Stratification factors will be the following: institution, modalities of adjuvant treatment (pre-operative alone versus post-operative versus none), number of mediastinal lymph node stations involved (0 vs. 1 vs. ≥2), histology (squamous cell carcinoma vs. others), use of pre-treatment PET-scan (Yes vs. no).

In conclusion, to randomise a new patient, one must fill the randomisation form via the Web and randomise through the web. If the centre has no access to the web, or in case of problem with the web connexion, one must fill the randomisation form and send it by fax at the following:

Web address to randomise: *https://fr.tenalea.net/igr/*
In case of impossibility to use the web, fax the randomisation to
Mrs : Gisèle Goma
Phone : 01 42 11 54 72 or BEEP 01 42 11 49 00 (from France)
Phone : 33 1 42 11 54 72 or BEEP 33 1 42 11 49 00 (from abroad)
Fax : 01 42 11 52 05 (from France)
Fax : 33 1 42 11 52 05 (from abroad)

After randomisation, a form will be sent back to the investigational centre to confirm if the patient will be treated in the control arm or in the PORT arm. Confirmation will be sent back by fax or e-mail.

Timing of randomisation/surgery and chemotherapy (if any) :

- In case of no post-operative CT, randomisation will be performed as soon as possible after histological results of complete surgery. Randomisation should take place within 6 weeks after surgery.
- In case of post-operative CT, randomisation should be performed as soon as possible after the last administration of CT (within 3 weeks) and no later than 6 months after surgery.

Timing of radiotherapy :

In patients allocated to RT arm, thoracic radiotherapy should start :

- in case of no post-operative CT , no sooner than 4 weeks after surgery *(and no later than 8 weeks after surgery*) **or**
- in case of post-operative CT, no sooner than 2 weeks after the last administration of chemotherapy *(and no later than 6 weeks after the last administration of chemotherapy)*

and, at the latest, within 3 weeks after randomisation. The interval between chemotherapy and radiotherapy may be extended to 4 weeks in case radiosensitizing drugs such as gemcitabine have been used. See Appendix 23.2 (a figure summarising the timing).

8 TREATMENTS

8.1 Surgery

Primary lung cancer should be resected completely and this may necessitate lobectomy, bilobectomy or pneumonectomy. For a lung resection to be defined as complete, the International Association for the Study of Lung Cancer (IASLC) staging committee has recently proposed a definition [Rami-Porta et al, 2005]. All resection margins, including bronchial, venous and arterial stumps and peribronchial soft tissue, should be microscopically free of

disease. A resection will be considered to be incomplete in case of tumour involvement of resection margins and/or positive cytology of pleural or pericardial effusion (refer to appendix on surgery if needed). **Lymph node exploration is mandatory** for the purpose of this study, as well as the description of the technique used. The surgeon may choose to use node sampling or systematic nodal dissection. Complete lymph node dissection involves removing all lymph nodes of the anatomically defined level. Lymph node sampling necessitates opening the pleura and removing representative tissue from each lymph node level. Whether a more extensive mediastinal exploration may result in improved survival remains an open question [Izbicki et al, 1998; Keller et al, 2000; Wu et al, 2002 Wright et al, 2006]. However a systematic nodal dissection or, at least a lobe-specific nodal dissection is recommended. Both the surgical report and the histological report should specify all the explored lymph node stations explored, and identify those containing metastases [Mountain, 1997, Watanabe et al, 1990]. According to the IASLC, even if complete dissection of all mediastinal tissue is desirable, systematic nodal examination should at least comprise 3 intrapulmonary and hilar nodes and at least 3 nodes from the following mediastinal nodal stations according to the location of the primary tumour:

- Right upper and middle lobe : subcarinal nodes (Station 7) and 2 of the following 3 stations superior paratracheal (station 2), inferior paratracheal and pretracheal (station 4)
- Right lower lobe : subcarinal nodes (Station 7) and right inferior paratracheal (station 4) and either the paraesophageal or pulmonary ligament nodes (stations 8 and 9)
- Left upper lobe : subcarinal nodes (Station 7) and subaortic and anterior mediastinal nodes (stations 5 and 6)
- Left lower lobe : subcarinal nodes (Station 7), paraesophageal and pulmonary ligament nodes (stations 8 and 9)

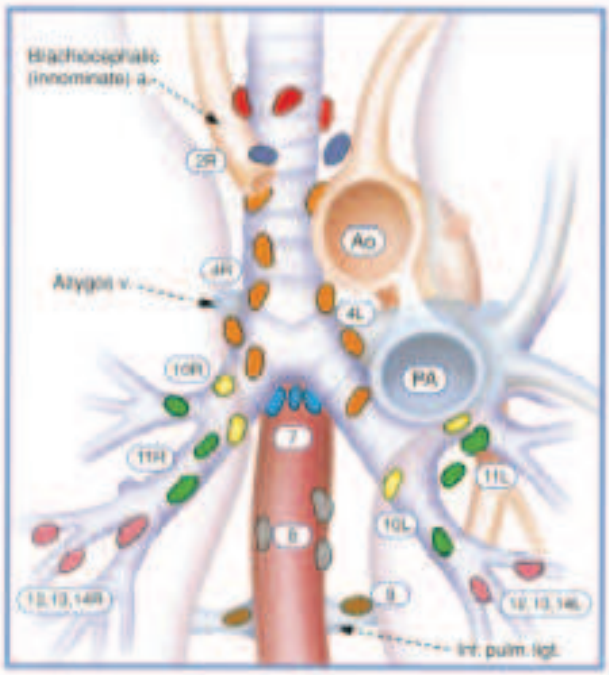
If extra-capsular nodal extension is identified in an isolated mediastinal node that is sampled, this will be considered as an incomplete resection. If there is extra-capsular nodal extension within a complete lymph node dissection, the patient may be included in the study as long as it is specified in the CRFs together with the nodal station concerned. The surgical report should describe in detail the lymph nodes which have been explored, and based on these reports (both surgical and histopathological), definition of sampling or dissection will be determined *a posteriori* for each individual patient included.
It is recommended to explore the following lymph node levels or stations systematically:

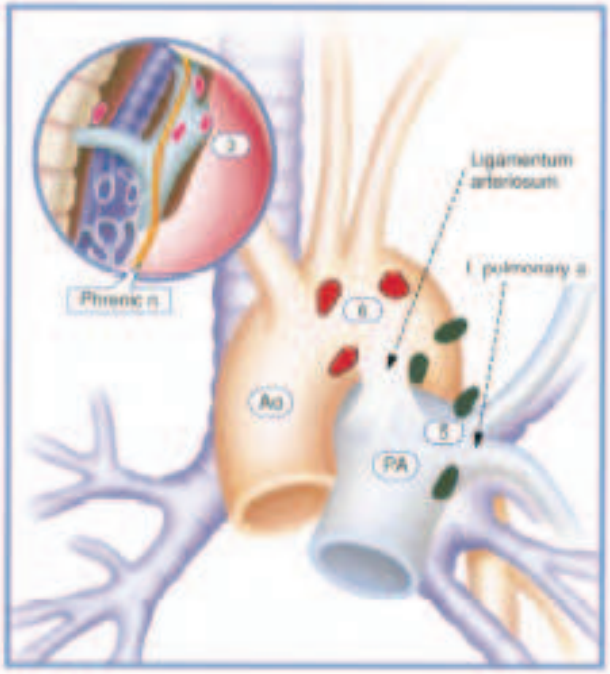
- Levels 2, 4 and 7 in case of upper/middle right-sided lung cancer;
- 4, 7, 8 and 9 in case of lower right-sided lung cancer;
- 5, 6, and 7 in case of upper left-sided lung cancer;

- 7, 8 and 9 in case of lower left-sided lung cancer as recommended [Rami-Porta et al 2005, Lardinois et al 2006]

Lymph Nodes levels will be defined according to the criteria of the joint AJCC and UICC classification shown on the following figure [Mountain, Chest 1997].

Patients having a bronchial margin with carcinoma in situ, or a pleural lavage positive cytology **should not be included**.





Superior Mediastinal Nodes

- 1 Highest Mediastinal
- 2 Upper Paratracheal
- 3 Pre-vascular and Retrotracheal
- 4 Lower Paratracheal (including Azygos Nodes)

N_1 = single digit, ipsilateral
N_2 = single digit, contralateral or supraclavicular

Aortic Nodes

- 5 Subaortic (A-P window)
- 6 Para-aortic (ascending aorta or phrenic)

Inferior Mediastinal Nodes

- 7 Subcarinal
- 8 Paraesophageal (below carina)
- 9 Pulmonary Ligament

N_1 Nodes

- 10 Hilar
- 11 Interlobar
- 12 Lobar
- 13 Segmental
- 14 Subsegmental

(Mountain/Dresler modifications from Naruke/ATS-LCSG Map)

8.2 Conformational post-operative radiotherapy

According to randomisation, patients will receive or not receive PORT.
We recommend that patients randomized in the treatment arm start PORT as soon as possible after randomisation as recommended on chapter 8.
No concomitant chemotherapy is allowed.

An interval of at least two weeks between the last administration *of* chemotherapy and PORT is mandatory. This interval may be extended in case radio-sensitizing drugs such as gemcitabine have been used, or when the patient does not have full haematological recovery after chemotherapy.
.

8.2.1 Radiotherapy technique

High-energy photons (≥6 MV) should be used. The planned dose to the ICRU reference point is 54 Gy in 30 fractions of 1,8 Gy or 27 fractions of 2 Gy. The radiotherapy will be given in once-daily fractions, 5 days per week**,** except in case of holidays or machine breaks. The corresponding overall treatment time is 37-39 days for 27 fractions and 40-42 days for 30 fractions. A delay in the overall treatment time up to 5 days will be considered as acceptable. The dose per fraction should never exceed 2 Gy**.** The use of conformal techniques is mandatory.
The field arrangement should use ≥ 2 beams. All fields should be treated daily. This protocol does not mandate any specific field arrangement to be used, however entry beams homolateral to the side of the tumor should be privileged.
Use of beam energies above 10 MV should be avoided given the increased lateral electron transfer in lung tissue at high energies [Senan et al, 2004]. Doses are to be calculated with heterogeneity correction, i.e., correction is to be made for density differences between air spaces, lung, water-density or bony tissue.
A planning CT scan in treatment position should be used, with a maximal slide thickness of five mm for the whole thorax. The use of intravenous contrast is recommended. All target volumes as well as the critical organs should be delineated on this CT scan.
Dose-volume histograms (DVH) of all target volumes (rCTV, CTV and PTV) and of all critical organs (lungs, cardiac volume, spine ± oesophagus) as described in the following section are required.
Intensity modulated radiotherapy (IMRT) is authorized in centres with IMRT expertise after discussion with the PI. All patients treated in an authorized centre should then be treated with IMRT

8.2.2 Definition of volumes

All lymph nodes should be outlined using a “mediastinal window” setting.

rCTV in the mediastinum (resected Clinical Tumour Volume). This corresponds to lymph nodes involved according to the pathological report of the lymph node exploration. The bronchial stump,

the homolateral hilar node region as well as the eventual extension to mediastinal pleura adjacent to the completely resected tumour bed will **always** be included in the rCTV.

CTV in the mediastinum (Clinical Target Volume). In the CTV, will be included the rCTV plus a margin for micro-extensions of nodal disease, which is 1.0 cm (**CTV=rCTV+1 cm**). We recommend the vertebral body to be excluded from the CTV. The upper and lower lymph node station to the involved lymph node regions should be included in the CTV, in case of sampling. The **volumes delineated for the CTV (CTV=rCTV+1cm) should not exceed the maximal upper and lower limits** as shown in the following table. **All the lymph nodes that lie between two non-contiguous node stations that are involved will be included in the CTV**. Because of the frequent involvement of sub-carinal (LN7) and homolateral paratracheal nodes (LN4) on surgical series, these stations will always be systematically included in the CTV.

The ipsilateral supraclavicular region will not be routinely included systematically in CTV.
The lymph nodes can be delineated according to the atlas from the University of Michigan [Chapet et al, 2005] corresponding to a CT-based definition of thoracic lymph node stations based on the Mountain and Dressler classification system.

Table of examples of CTV according to LN involvement (text in bold is meant to specify a station containing metastatic nodes)

Surgically involved mediastinal nodes	LN stations to be included in the CTV
1-2R	1-2R,4R,7,10R Maximal upper limit : 1 cm above sternal notch but homolateral subclavicular node station may be treated if needed Maximal lower limit : 4 cm below the carina* (unless other nodes are involved)
1-2L	1-2L,4L,7,10L Maximal upper limit : 1 cm above the sternal notch but homolateral subclavicular node station may be treated if needed Maximal lower limit : 4 cm below the carina*
3 (Right sided Tumour)	**3**,4R,7,10R Maximal upper limit : 1 cm above the sternal notch Maximal lower limit : 4 cm below the carina*
3 (Left sided Tumour)	**3**,4L,7,10L

	Maximal upper limit : 1 cm above the sternal notch Maximal lower limit : 4 cm below the carina*
4R	**4R**,7,10R Maximal upper limit : sternal notch Maximal lower limit : 4 cm below the carina*

4L	**4L**,7,10L Maximal upper limit : sternal notch Maximal lower limit : 4 cm below the carina*
5	4L,**5**, 7,10L Maximal upper limit : Top of aortic arch Maximal lower limit : 4 cm below the carina*
6	4L, **6**,7,10L Maximal upper limit : sternal notch Maximal lower limit : 4 cm below the carina*
7 (Right sided Tumour)	4R,**7,**10R**.** Maximal upper limit : Top of aortic arch Maximal lower limit : *5* cm below the carina*
7(Left sided Tumour)	4L, **7,** 10L Maximal upper limit : Top of aortic arch Maximal lower limit : *5* cm below the carina*
8 (Right Tumour)	4R,7, **8,** 10R**.** Maximal upper limit : Top of aortic arch The maximal lower limit should be the gastro-oesophageal junction
8 (Left sided Tumour)	4L,7,**8,**10L**.** Maximal upper limit : Top of aortic arch The maximal lower limit should be the gastro-oesophageal junction

* (unless other nodes are involved)

PTV (Planning Target Volume). Due to organ movements as well as set-up uncertainties an additional margin of at least 0,5 cm (lateral, anterior and posterior) and 1 cm (superior and inferior)

is recommended. The margins may be individualised according to 4D-CT scan data and / or measurements of the daily set-up error.

8.2.3 Critical organs

Spinal cord : The maximal dose should be 45 Gy. The inner margin of the bony spinal canal will be considered as being the boundaries of the spinal cord.

Lungs : The lung(s) will be contoured separately. A lung Dose-volume histogram (DVH) will be required. The V20 is computed on the lung(s) volume *minus* the PTV. The V20 should not exceed 31% after lobectomy and 22% after pneumonectomy (In the post-operative setting, no data are available about the predictive value of DVH parameters and lung toxicity. We therefore modified the V20 data of Graham et al (table 6) in a conservative way, taking into account the reduction of lung capacity by the surgical resection). Lung DVH (V20, V5) and mean lung dose should be specified. The dose of 5 Gy or more given to the total lung volume has been recently described as potentially more predictive of late lung toxicity

Table 6 : Risk of radiation pneumonitis after exclusive radiotherapy (≥ grade 2 RTOG scale)

V20 Gy	Risk of radiation pneumonitis **≥ gr 2**
<22%	0%
22-31%	7%
32-40%	13%
>40%	36%

Oesophagus : Contouring the oesophagus is mandatory. The oesophagus volume *(outer muscular contour)* must be contoured from the level of just below the larynx to the gastro-oesophageal juncture. The total volume of the oesophagus shall be contoured and the PTV should NOT be subtracted from this volume. The mean oesophageal dose as well as the maximum oesophageal dose should be recorded.

Heart : The dose to 30% of the cardiac volume should not exceed 35 Gy. Contouring the heart will be mandatory.

8.3 Other treatments

Patients may take their usual medication, as well as steroids if prescribed. Prophylactic cranial irradiation may be delivered to patients. However, no concomitant chemotherapy will be administered during thoracic radiotherapy.

8.4 In case of progression

- Patients should be treated according to their institution's standards.
- All information concerning progression or recurrence will be collected.

9 FOLLOW-UP AND END-POINTS

9.1 End-Points

The starting date for any time dependant end point will be the date of randomisation.

9.1.1 Main End-point

- Disease-Free Survival (events: local recurrence and metastases, death of any cause) evaluated with a minimal follow-up of 3 years in all patients.

9.1.2 Secondary End-Points

- Evaluation of treatment complications rates (early complications occurring during radiotherapy or within 90 days after the end of radiotherapy, will be evaluated with CTCAE v3.0 scale. Late effects of treatment will be evaluated yearly with CTCAE v3.0 scale)
- Patterns of failure : proportion of local failure (within or outside the radiotherapy fields), metastases, both and intercurrent deaths among the disease-free survival events
- Cumulative rate of local failure (within or outside the radiotherapy fields), metastases, and second cancers
- Analyses of prognostic factors and predictive factors of treatment effect on disease-free and overall survival, and predictive factors of treatment-related toxicity
- Overall Survival (events : death of any cause)
- Cost for each year of life with no recurrence gained (exclusively in French participating centres)

These criteria will be evaluated with a minimum follow-up of 3 years for all patients.

9.2 FOLLOW-UP

Patients will be evaluated 3 and 6 months after randomisation. Thereafter, patients will be evaluated every six months for the first three years after randomisation and yearly afterward. All patients should be followed until death. A CT-scan of the chest, preferentially with intravenous contrast, is required every 6 months during the first 3 years and yearly thereafter, until disease progression. Other exams are optional.

Patients should undergo a yearly cardiac ultra-sound and lung function tests (FEV1 and DLCO) until disease progression. Centers unable to comply with the yearly cardiac ultra-sound follow up, recommended to detect cardiac toxicity, should contact the principal investigator to discuss alternative solutions.

When a grade 3 or higher side effect (cardio-vascular or pulmonary) occurs, a chest CT-scan preferentially with intravenous contrast, a cardiac ultra-sound and a lung function test (FEV1 and DLCO) should be performed.
For each patient included, the following forms will be required. The calendar of follow-up is described on pages 10 and 11.

- Just before randomisation : randomisation form, initial work-up forms and baseline, cardio-pulmonary function and toxicity form
- 3 months after randomisation : treatment form, follow-up form and toxicity form
- 6 months after randomisation : follow-up form, and toxicity form
- Yearly (1 year after randomisation) : follow-up form, cardio-pulmonary function form and toxicity form*, for at least 5 years.* It is highly recommended to follow-up patients until death. After 5 years, we encourage investigators to keep track of their patients, if necessary with the help of a general practitioner. or through cancer or death registry.
- In case of event (local recurrence, metastasis, toxicity grade 3 or more, second cancer, death) : an event form

10 REPORTING OF SERIOUS ADVERSE EVENTS (SAE) AND LATE TOXIC EFFECTS

10.1 Definition

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose :

- Results in death
- Is life-threatening
- Requires patient hospitalisation or prolongation of existing hospitalisation
- Results in permanent disability or serious temporary incapacity
- Results in congenital abnormality/birth defect or abortion
- Is medically significant

The terms disability and incapacity mean any temporary or permanent physical or mental disability that is clinically significant and that has an important effect on the patient's physical activity and/or quality of life.

Any clinical event or laboratory result considered serious by the investigator and not corresponding to the criteria of seriousness defined above is nevertheless considered to be medically significant. Such an event/result may carry a risk for the patient and may require medical intervention to prevent one of the outcomes listed above.
Example: overdoses, second cancers, pregnancies and new facts can be considered medically significant.

The following are not considered to be serious adverse events (SAE) :

- Hospitalisation < 24 hours,
- Hospitalisation planned prior to the beginning of the trial and/or taken into account in the protocol (e.g. biopsy, chemotherapy).

10.2 Intensity criteria

Intensity criteria must not be confused with criteria for seriousness, which serve as guidelines for the definition of obligations for declaration.

Intensity of events will be assessed according to the NCI-CTCAE classification, version 3.0 (toxicity score from 1 to 5, appendix). Intensity of adverse events not listed in this classification will be assessed according to the following terms:

Mild (1): does not affect the patient's usual daily activity
Moderate (2): perturbs the patient's usual daily activity
Severe (3): prevents the patient carrying out his/her usual daily activity
Very severe (4): requires intensive care or is life-threatening
Death related to this AE (5)

10.3 Instructions in case of SAE

Any SAE as defined above which occurs or comes to the attention of the investigator at any time during the study and through 30 days after the last administration of studytreatment, independent of the circumstances or suspected cause, must be reported immediately, within 24 hours of knowledge via a SAE form to:

UF pharmaco-vigilance at IGR:
Tel: +33 (0)1 42 11 61 00 (09:00 – 18:00 Monday to Friday, except bank holidays)
Fax: +33 (0)1 42 11 61 50 **Email**: phv@igr.fr

The Pharmacovigilance Unit at IGR will assess the adverse events in terms of seriousness, expectedness, severity (NCI-CTCAE v3.0) and relationship to the study treatment. All SAEs will be coded using medDRA.
Assessment of causality of SAEs may be reviewed during the study by the study coordinator.

All late Serious Adverse Events (occurring after this period of 30 days) considered to be reasonably related to the study treatment(s) or the research must be declared (no time limit).

Information collected in the SAE form is crucial to assess the case and for this reason diligence in collecting as much verifiable and reliable information: BOTH QUALITY and TIMELINES are key factors.

The investigator must provide any relevant information for the required 8 days follow up report for any SAE which is fatal or life threatening.

As far as possible, for each event, the following should be noted:

1) A description as clear as possible, using medical terminology,
2) Its duration (start and end dates),
3) Action taken and the need for corrective treatment or not, discontinuation of study treatment(s) or not, etc.,
4) Its intensity (grade 1-5), according to the NCI/NIH Common Toxicity Criteria version 3.0 (a copy of the CTCAE version 3.0 can be downloaded from the CTEP home page : http://ctep.info.nih.gov)
5) Its relationship to the study drug or treatment, the disease treated, another disease or another treatment, or to a constraint linked to the research (period without treatment, further tests required for the research, etc.,)
6) Documentation of all co-medication and/or therapies,
7) Documentation of all relevant medical history and/or co-existing diseases
8) The outcome (where applicable). For non fatal events, developments should be followed-up until either recovery or recovery of a previous state of health or the stabilisation of possible sequelae.

The investigator must also attach the following to the serious adverse event report form, whenever possible :

- A copy of the summary of hospitalisation or its prolongation,
- A copy of the post-mortem report, (when applicable)
- A copy of all laboratory examinations and the dates on which these examinations were carried out, including relevant negative results, as well as normal laboratory ranges,
- Any other document that the investigator judges useful and relevant.

All these documents will remain anonymous.

Nevertheless, any event that is expected but that is different in terms of intensity, evolution or frequency will be considered to be unexpected by the Pharmacovigilance Unit.

10.4 SAE follow-up

The investigator is responsible for the appropriate medical follow-up of patients until resolution or stabilization of the adverse event or until the patient's death. This may mean that follow-up should continue once the patient has left the trial.

Follow-up information about a previously reported serious adverse event must be reported by the investigator to the Pharmacovigilance Unit within 48 hours of receiving it (on the serious adverse event report form, by ticking the box marked “Follow-up N°…”). The investigator must also transmit the final report at the time of resolution or stabilization of the SAE. The investigator retains the documents concerning the supposed adverse event so that previously transmitted information can be completed if necessary.

11 BIOLOGICAL STUDY

For clinicians, a better understanding of the molecular events underlying treatment’s efficacy or inefficacy as well as normal tissue injury may allow a more rational approach to treatment. This study is described in the appendix ***23.4***. It is mandatory for the participating centres, but of course patients may accept to participate in the trial but decline to participate to the biological study.
To facilitate the work of the centre, a pre-paid DHL package is provided for each patient blood samples. For each tumor block, the pathologist of the coordinating centre will contact directly the pathologist of the participating centre (see appendix 23.4).

12 ECONOMIC STUDY

This study will be done exclusively in France, except if other national groups choose to participate to the economic evaluation. It is described in the appendix ***23.9.***

13 SAMPLE SIZE

In the IALT study, the local recurrence rate at 3 years among pN2 patients (whether or not they have had chemotherapy) is 34%. The disease-free survival in this subgroup of patients is 29% at 3 years.
For the present study, considering the 3-year-disease free survival is 30%, if we want to observe 10 % absolute improvement of disease-free survival, in the PORT arm (i.e. 40% at 3 years), 430 events should be observed (local or distant recurrence, death of any cause) so that 660 patients followed up for a median follow-up of 3 years are necessary (power of 80%, significance of 5%, bilateral test, logrank). With a longer follow-up (median of 5 years), this sample size could also allow

to show a difference in terms of survival rate of 9% at 5 years (from 22% in the control arm to 31% in the investigational arm).

Thus, we propose to include 700 patients in our study. Participation of many centres is important so that the planned duration of the trial will not be too long. The table below shows the duration of the trial according to different inclusion durations.

Inclusion duration	3 years	4 years	5 years
Minimum Follow-up	1.5 years	1 year	0.5 years
Median Follow-up	3 years	3 years	3 years
Duration of the whole study	4.5 years	5 years	5.5 years

This trial should be conducted at an international level with the participation of different national cooperative groups like the *Intergroupe Francophone de Cancérologie Thoracique* (IFCT) in France, the *Lung Adjuvant Radiotherapy Spanish Group* in Spain, and possibly other national groups as well as the EORTC.

14 STATISTICAL ANALYSIS

Disease-free survival and overall survival rates will be compared between the two groups using Cox model adjusted on the stratification factors. Some regrouping of stratification strata may be necessary depending on the final distribution. The origin of time will be the date of randomisation and the median follow-up for analysis will be 3 years. An analysis of prognostic factors for disease-free and overall survival will be performed. The variation of the effect of radiotherapy with the stratification factors will be studied.

The rate of early complications will be compared between the two arms with a logistic model adjusted on stratification factors. The rate of late sequelae will be compared with models taking into account the repetition of data with time and possibly the stratification factors. These models will also be used to study the variation of toxicity with gene polymorphisms by adding interactions with treatment and by taking into account the multiplicity of analyses.

14.1 Protocol deviations

No exclusion will be allowed. Randomised patients who do not fulfil the eligibility criteria and those who do not comply with the protocol will all be included in the analysis in their randomisation arm (intention to treat analysis).

In order to minimise the number of patients lost to follow-up, each investigator will be responsible for re-contacting the patients who do not come to the follow-up visits.

14.2 Intermediate analysis and monitoring

An independent Data Monitoring Committee (DMC) composed of international experts (at least 2 clinicians and 1 statistician) will be constituted and meet once or twice annually. It will carefully watch accrual rate and toxicity and examine interim analyses in the light of the results of similar trials. Data on non-cancer mortality (toxic and other causes of death), and grade 3,4 late toxicities in both arms of the study will be provided yearly to the DMC. Yearly cardiac ultra-sound and lung tests will help to detect some of the pulmonary and cardiac toxicities that may occur.
Provided the DMC agrees, one interim analysis should be performed and take place after the occurrence of 215 events (local or distant recurrence, death of any cause).
The DMC will propose to the Steering Committee to stop accrual or to publish preliminary results earlier than anticipated only if one of the following conditions is met :

- the results of the interim analysis show clearly ($p<0.001$) that PORT is beneficial (increase of disease-free survival) or harmful
- all the data from this or other ongoing trials are convincing enough to influence the practice of most physicians.

15 ETHIC AND REGULATORY ASPECTS

The clinical trial is to be carried out according to the ethical principles of the Helsinki Declaration of 1964, revised in Edinburgh in 2000, to Good Clinical Practice as defined by the International Harmonisation Conference (ICH–E6, 17/07/96), the European Directive (2001/20/EC) on the performance of clinical trials, and in agreement with local ethics requirements in each Member State in which the clinical trial will be conducted.

15.1 Ethic Committee

Before the clinical trial starts, the Ethics Committee should give its opinion about the trial. It is the sponsor's responsibility to submit all the documentation required to the Ethics Committee as defined in the detailed guidance of the requirements of Directive 2001/20/EC and according to each Member State requirements.

In this case, a multicentre clinical trial carried out in different countries, a single opinion should be given for each Member State concerned by the clinical trial.

15.2 Participant Information and Consent Form

Prior to any biomedical research being carried out on any individual, the latter is required to give his/her specific informed consent in an entirely free manner once he/she has been given all necessary information by the investigator or his/her representative concerning the aim of the research, the duration of the study and the way in which it will be carried out, its benefits, potential

risks and constraints, together with the nature of the product being tested and the opinion given by the Ethics Committee.

The consent form is to be signed and dated personally, both by the patient and the investigator, or by the doctor representing the latter (the original is to be archived by the investigator and a copy to be given to the patient or his/her legal representative).

A single document is to be used for patient information and informed consent, in order to avoid any risk of dispute concerning the content of the information supplied., there is one sample of patient information letter and informed consent letter to be adapted according to each country legislation.

16 QUALITY ASSURANCE (QA)

The sponsor is responsible for setting-up a quality control system, as described in internal procedures, so that the trial may be carried out according to the terms of the protocol and in line with Good Clinical Practice. During the trial, the sponsor can audit an investigational site or one of the related CRO if considered necessary. The investigator will be informed in advance by a letter about the audit date and the items that will be audited.

16.1 Conformal Radiotherapy Assurance Programme

In order to implement this QA protocol, funding will be needed so as to have an independent QA control.
Conformal radiotherapy carries inherent problems both in ensuring reproducibility and accuracy within a radiotherapy unit and, more particularly, when carried out on a multi-centre basis. In this multi-institutional randomised trial the quality assurance programme (QA) will enable confirmation that technical guidelines within the protocol have been understood and implemented correctly by participants and that the dose prescription is delivered according to protocol with appropriate documentation.

The excess of toxicity (mostly cardiac and pulmonary) and non-cancer related deaths observed in the post-operative radiotherapy arm of the trials included in the meta-analysis can probably be explained by excessive volumes of radiation, old radiation techniques, too large doses and fraction sizes. The hazards of such toxicities have been highlighted, but of equal concern is the question of tumour recurrence if inadequate treatment is given. These factors emphasise the importance of treatment technique in the present trial and the need for external quality assurance to avoid major clinical problems and to ensure equivalence of techniques.

The programme will proceed as follows :

1) Before entering any patient into the trial, one dummy-run test will be performed within each participating centre. It will correspond to a post-operative chest CT-scan: either post-lobectomy or post pneumonectomy. This scan will be available on the QA website together with patient clinical

data (surgical, pathological report) to be used for treatment planning. The EQUAL-ESTRO RT Quality Assurance Team will contact new investigational centres (equal-estro@equal-estro.org) and provide them a securized access to the website.

Thus all potential investigators will have to define according to the protocol guidelines :

- Target volume and treatment technique used
- Delineation of organs at risk (heart, lungs, esophagus)
- Planning of radiation distributions across the treatment volume for homogeneity
- Dose-volume histograms (DVH) of all target volumes (rCTV, CTV and PTV) and of all critical organs (lungs, cardiac volume, spine and oesophagus)

Routine quality control performed by the centre will be assessed and compared with protocol guidelines.

2) The dummy-run test will be sent back to the QA team to validate treatment planning. This will eventually be followed by discussions between QA team and the investigators in case of non-conformity to the protocol guidelines

3) The plans for the first patient included in the radiotherapy arm, from each participating centre, together with verification images will be collected by the QA team.

4) Subsequently, for 15% of patients randomly selected, plans as well as verification images will be collected by the QA team to ensure continued protocol adherence in centres where plans of the first patients were adequate, whereas all plans will be considered for revision in the centres where plans were not adherent to the protocol.

5) Informations concerning dose to planning target volume and organs at risk are collected in the radiotherapy CRF form for all patients.

Dose to planning target volume (PTV) and organs at risk

	PTV	Lung	Heart	Spinal cord	Esophagus*
Volume (cm^3)	|___|___|___| volptv	|__|__|__|__| volung	|__|__|__| volheart	|__|__|__| volcord	|__|__| leneso
Minimal dose (Gy)	|__|__|•|__| minptv	|__|__|•|__| minlung	|__|__|•|__| minheart	|__|__|•|__| mincord	|__|__|•|__| mineso
Maximal dose (Gy)	|__|__|•|__| maxptv	|__|__|•|__| maxlung	|__|__|•|__| maxheart	|__|__|•|__| maxcord	|__|__|•|__| maxeso
Mean dose (Gy)	|__|__|•|__| meanptv	|__|__|•|__| meanlung	|__|__|•|__| meanheart	|__|__|•|__| meancord	|__|__|•|__| meaneso

* *Length in cm*

PTV dose to 95% volume (Gy) ..... ptv95 |___|___|•|___|

Percent lung volume receiving ≥20 Gy ..... lung20 |___|___|

Percent heart volume receiving ≥35 Gy ..... heart35 |___|___|

Esophagus length receiving ≥50 Gy (cm) ..... eso50 |___|___|

6) On a voluntary basis, clinicians will be invited to provide paper copies of the treatment plan of all patients included into the radiotherapy arm and send to the PI of the study

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Paper copies of transversal, sagittal and frontal planes at the centre of PTV, HDV (lung(s), heart, oesophagus, spinal cord), DRR of every field and radiation port films should be sent for every patient except for the first patient included (QA by Equal ESTRO).These data will be very useful as their analysis may help to better understand factors contributing to cardio-pulmonary toxicity.

Analysis of QA programme

The data from the quality assurance programme will be analysed separately from the main trial. Major discrepancies from trial protocol will be notified to participating centres.

These will include:

1) Discrepancies in documentation, dose prescription and dose recording
2) Inadequacy between treatment planning and treatment delivery
3) No respect of dose constraints to the organs at risk
4) Systematic errors of technique in any stage of treatment from planning through to implementation

More detailed analysis of the quality assurance data will enable :

1. An independent review of variations in conformal mediastinal radiotherapy practice in participating centres.
2. Quantification of dose uniformity during the treatment period.
3. Correlation of physical parameters of radiation with trial end points :
   - The association between dose variation across the treatment volume and tumour control
   - Variations in dose homogeneity with late sequelae
   - Predictive factors of toxicity

16.2 Surgical Quality Assurance Programme

A surgical advisory committee, composed of international experts, will meet regularly to check for the quality of surgery. This is the reason surgical and pathological reports are requested for each patient included.

17 RESPONSIBILITIES

17.1 Investigator's responsibilities

The principal investigator in each of the establishments concerned undertakes to conduct the clinical trial according to the protocol approved by the Ethics Committee. The investigator may not change any of the terms of the protocol without approval from the sponsor and the agreement of the Ethics Committee.

The principal investigator is responsible for :

- Providing the sponsor with his/her own CV and those of the co-investigators ;
- Identifying those members of his/her team who are to participate in the study and defining their responsibilities ;
- Ensuring, as far as possible, that the required numbers of patients are enrolled in the trial, within the time period established for such inclusion.

Each investigator is responsible for :

- Collecting informed consent forms, duly signed and dated by the patients, prior to any specific trial selection procedures ;
- Regularly completing Case Report Forms (CRF) for all patients included in the trial, and ensuring that the Clinical Research Assistant (CRA) has direct access to all the original documents, so that the latter may validate observation sheet data ;
- Dating, correcting and signing CRF corrections for all trial patients ;
- Agreeing to regular visits from the CRA, and where applicable, those of auditors appointed by the sponsor or inspectors from the supervisory authorities.

All documents relating to the study (protocol, consent forms, CRFs, the investigator file and so on), together with original documents (laboratory results, x-rays, consultation reports, clinical examination reports, etc.) are to be kept in a safe place and are to be considered as confidential. Archiving of data will be the investigator's responsibility and is to be carried out according to legislation currently in force. The investigator must keep the study data together with a list of patients for at least 15 years after the end of the study.

17.2 Sponsor's responsibilities

In accordance with the Directive 2001/20/EC requirements, it is the sponsor's (IGR) responsibility :

- To take out civil liability insurance against consequences of the research that may be prejudicial for the person taking part in it ;
- To submit all the documents required to the Ethics Committee (EC) and the Competent Authority (CA) according to local requirements ;
- To obtain the approval from the Ethics Committee and the Competent Authority before starting the trial ;
- To inform the managers of the health institutions ;
- To transmit all information relevant to the management of the research to the investigators ;
- To provide sufficient material to permit the investigators to conduct the trial according to the agreed protocol.

The sponsor may delegate any of his trial-related functions to an individual, a company, an institution or an organisation. However, in such cases the sponsor remains responsible for ensuring that the trial conduct and the final data generated comply with the requirements of Directive 2001/20/EC.

The sponsor must ensure that documents vital to the running of the trial are safely archived for the minimum 15-year period provided for by Good Clinical Practice guidelines, that is to say, 15 years after the end of the research activity.

18 ORGANISATION

The Co-ordinating Centre will be responsible for randomisation and day to day management of the trial.
The Steering Committee will include, besides members of the Co-ordinating Centre, investigators representing various specialities or co-operative groups. It will be responsible for the major organisation and policy decisions including the possibility of premature closure of the trial.
The independent Data Monitoring Committee will monitor the progress of the study on ethical and scientific grounds. It will periodically advise the Steering Committee on continuation or closure of accrual based on the progression of the trial and of scientific knowledge concerning the evaluated treatment.

19 DATA PROTECTION AND CONFIDENTIALITY MANAGEMENT

With regards to himself/herelf as well as all the persons involved in the trial, the investigator is responsible for insuring the confidentiality of the totality of the information supplied by the Institut Gustave Roussy (IGR) until the trial results are published. This obligation holds neither for the information that the investigator may communicate to the patients within the context of the trial nor the already published information.

The investigator commits not to publish, not to spread or use in any manner, directly or indirectly, the scientific and technical information related to the trial.

Nevertheless, in conformity with the article R 5121-13 of the Public Health Code, both the centre and the investigator may communicate information relative to the trial :

- to the Health Minister,
- to the public health inspectors who are doctors,
- to the public health inspectors who are pharmacists,
- to the Afssaps General Director and inspectors.

The trial cannot be the subject of any written note or oral comment without the prior agreement of the sponsor; the totality of the information that are communicated or obtained during the course of the trial appertains in full right to the Institut Gustave Roussy that can freely use it.

20 PUBLICATION OF RESULTS

All information resulting from this trial are considered to be confidential, at least until appropriate analysis and checking has been completed by the sponsor, the coordinating investigator and the statistician of the trial.

Any publication, abstract or presentation comprising results from the trial must be submitted for examination and approval to the Sponsor (IGR) and Steering Committee.

The first author of the publication will be the coordinating investigator, he/she may however designate another person to write the publication.

The other co-authors will be :

- investigators of the main recruiting centres listed in order of decreasing number of included patients,
- a member of each co-investigating group,
- the statistician of the trial,
- a sponsor's representative.

Furthermore, any written communication or presentation must imperatively include a section that mentions the IGR, and any institution, investigator, cooperating or collaborating group and scientific society that has contributed to the trial as well as any organism that has financially supported this research. The final publication will be made in the name of the Lung ART collaborative group ; however, all of the participating groups will be clearly indicated.

In an equal manner, publication of the sub-studies (biological studies, medico-economic study…) will make mention of the name of the person who has carried out the sub-studies as well as the names of all the persons who have taken part in carrying out these sub-studies.

21 PATIENT COMMITTEE

This protocol has been read by the French Federation of Patient Committees for Clinical Research in Cancerology (*Fédération des Comités de Patients pour la Recherche Clinique en Cancérologie* FCPRCC) of the FNCLCC (Fédération Nationale des Centres de Lutte Contre le Cancer) and of the French League for Treating Cancer (*Ligue Nationale Contre le Cancer*). This Committee read the protocol and suggested improvements, notably in relation to the information letter, availability of treatment and supervisory plans and patients' comfort and this, according to the charter agreed between the National League Against Cancer's Patient Committee and the FNCLCC clinical studies department.

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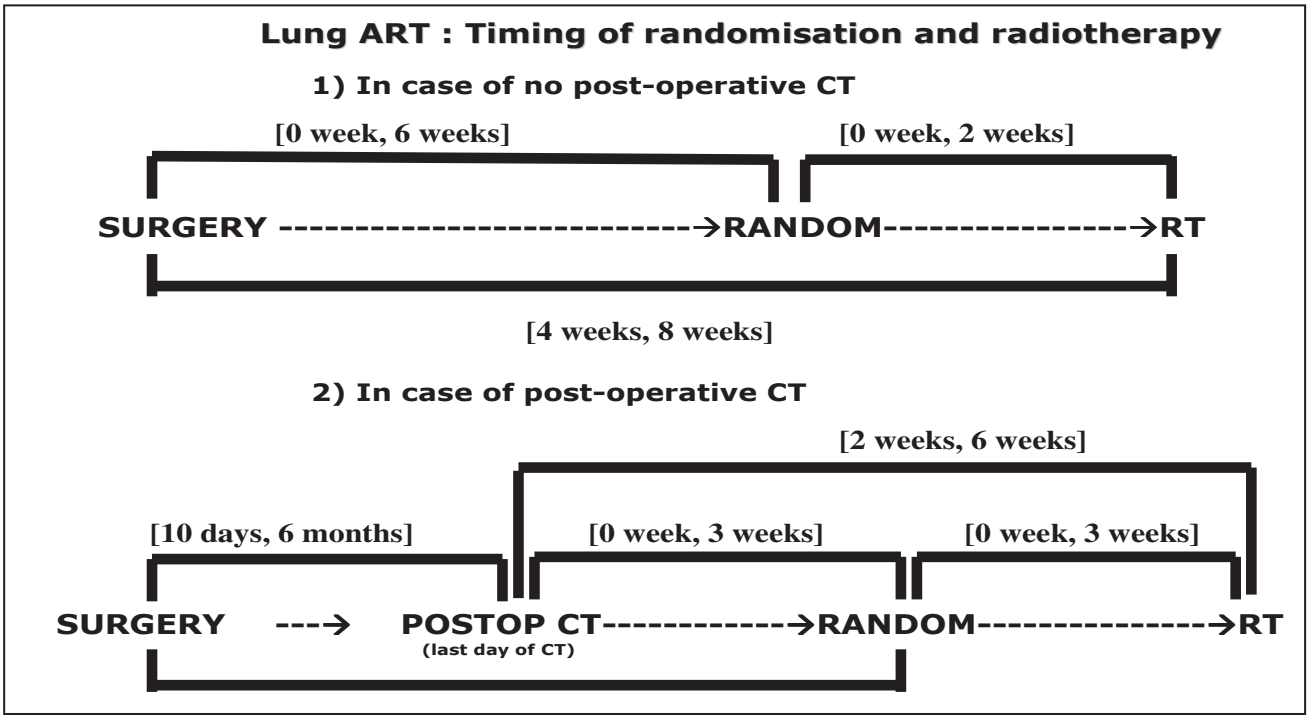
23 APPENDIX

22.1 Timing of randomisation and radiotherapy



6 months maximum

22.2 Technical appendix : Surgery and Pathology

Guidelines for the drafting of the surgical report

It should mention the following items:

1. **T factor**
   - 1.1 Description of “in situ” tumoral conditions and connections with surrounding structures
   - 1.2 Detail of extensions to the chest wall, mediastinal structures, and/or adjacent lobe in case of (bi-) lobectomy
   - 1.3 Technical aspects of the extended resections: resection “en bloc” or separate resection
   - 1.4 Report on accidental opening of the tumoral interface and possible spilling of the operative field.
2. **N factor**
   - 2.1 Type of lymphadenectomy according to the ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer [Lardinois et al.2006] systemactic lymph node sampling, lobe specific lymph node dissection, systematic lymph node dissection, extended lymph node dissection.
     Systematic nodal dissection or at least lobe-specific systematic nodal dissection is advised.
   - 2.2 Isolation and identification of lymph nodes harvested at the upper and lower limits of the lymph node dissection or sampling (proximal and distal lymph node stations in the cephalad to caudal direction)
3. **General**
   - 3.1 Delineation by metallic clips of zones where the resection could be microscopically incomplete. ***For the purpose of Lung ART study, if the pathological report confirms the resection is incomplete, the patient is not eligible.***
   - 3.2 Listing and results of frozen sections
   - 3.3 Description of an orientation of the operative specimen by marking of the resection margins
   - 3.4 Final statement on the completeness of the resection at the end of the operation (macroscopic findings and frozen section results)

Accurate intraoperative surgical staging should be insured by strict attention to the anatomic boundaries between nodal groups. Lymph Nodes levels will be defined according to the criteria of the joint AJCC and UICC classification shown on the following figure [Mountain, Chest 1997].

All ipsilateral lymph node levels 11-13 should be removed en bloc with the primary surgical specimen.

A pathologically complete surgical resection of the tumour mass by lobectomy, bi-lobectomy or pneumonectomy as needed will be performed. This may need extended resections: resection “en

bloc" or separate resection: this should be specified. A complete mediastinal lymph node dissection or nodal sampling must be performed.

Complete lymph node dissection is recommended. According to the IASLC, even if complete dissection of all mediastinal tissue is desirable, systematic nodal examination should at least comprise the following mediastinal nodal stations according to the location of the primary tumour:

- **Right upper and middle lobe**: superior paratracheal (station 2), and inferior paratracheal and pretracheal (station 4) and subcarinal nodes (Station 7)
- **Right lower lobe** : right inferior paratracheal (station 4), subcarinal nodes (Station 7) and, the paraesophageal and/or pulmonary ligament nodes (stations 8 and/or 9)
- **Left upper lobe**: subaortic and anterior mediastinal nodes (stations 5 and 6) and subcarinal nodes (station 7)
- **Left lower lobe**: subcarinal nodes (Station 7), paraesophageal and pulmonary ligament nodes (stations 8 and 9)

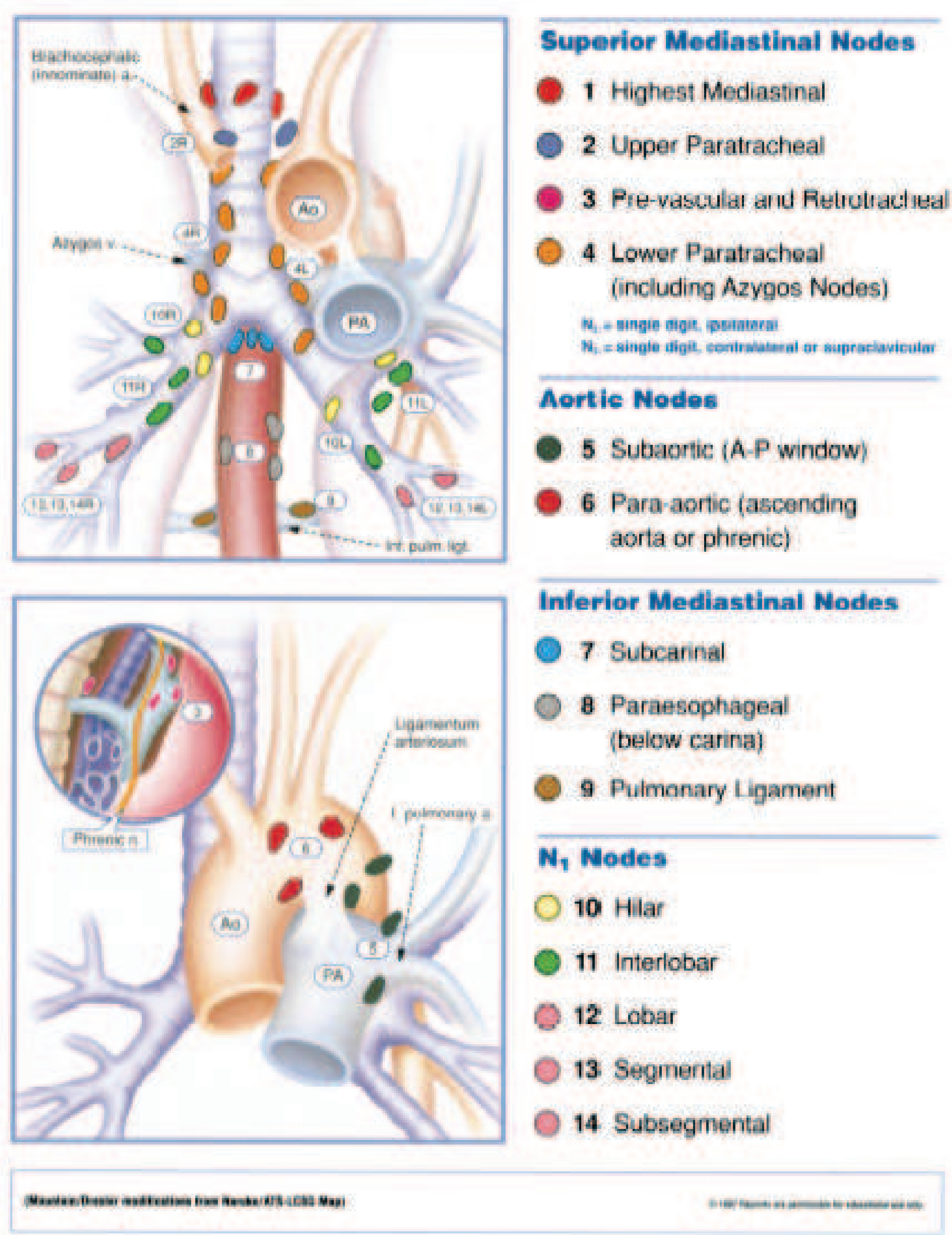
- Complete lymph node dissection involves removing all lymph nodes of the anatomically defined level or station. Thus several nodes may be explored in a single lymph node station (or level).

  Example: a patient with a right upper lobe tumour may have:
  - 0 nodes involved out of 2 explored nodes in lymph node station 2,
  - 2 nodes involved out of 3 nodes explored in lymph node station 4 and
  - 1 involved node out of 3 nodes explored in station 7.

  In conclusion, this patient will have 8 explored mediastinal nodes, 3 involved mediastinal nodes but two mediastinal node stations involved (station 4 and 7).

- Lymph node sampling necessitates opening the pleura and removing representative tissue from each lymph node level. All nodal tissue obtained must be carefully labelled by lymph node level by the operating surgeon in the operating room.

In addition, any lymph nodes which are not mentioned above but which appear grossly abnormal at surgery should be removed and their locations identified. The presence or absence of evidence of invasion of the nodal capsule should be noted on the pathology reports for mediastinal nodes. If there is evidence of extra-capsular extension in an isolated sampled node, this will be considered as an incomplete resection.


Brachiocephalic (innominate) a.
Azygos v.
2R
4R
Ao
4L
PA
10R
11R
7
8
10L
11L
9
12,13,14R
12,13,14L
Inf. pulm. ligt.
Ligamentum arteriosum
Phrenic n.
6
5
Superior Mediastinal Nodes
1 Highest Mediastinal
2 Upper Paratracheal
3 Pre-vascular and Retrotracheal
4 Lower Paratracheal (including Azygos Nodes)
Aortic Nodes
5 Subaortic (A-P window)
6 Para-aortic (ascending aorta or phrenic)
Inferior Mediastinal Nodes
7 Subcarinal
8 Paraesophageal (below carina)
9 Pulmonary Ligament
N1 Nodes
10 Hilar
11 Interlobar
12 Lobar
13 Segmental
14 Subsegmental

22.3 Appendix : LUNG ART BIOLOGY (LABIO)

Writing Committee : C. Capoulade Metay, E. Deutsch, A. Dunant, P. Fouret, D. De Ruysscher, J.P. Pignon.

22.3.1 Introduction

LUNG ART gives us the opportunity to increase our knowledge about factors that may predict for the potential benefit of adding radiotherapy to surgery on one hand, and radiation-induced toxicity on the other hand.

In a population that would have exactly the same modalities of thoracic irradiation (in terms of dose, volume, fractionation, amount of normal lung parenchyma irradiated, etc), it has been known for several decades that some patients are particularly prone to develop severe side effects due to radiotherapy, whereas others seem to be rather resistant. The molecular basis of this inter-individual variability is being elucidated in recent years. One of the most promising techniques to identify individuals with a high likelihood to develop severe radiation-induced damage is the analysis of germline polymorphisms in the DNA of circulating lymphocytes. Germline polymorphisms are inherited genetic variants that are present in all cells of the body. About 1.4 million such variants in differing frequencies have been identified thus far. In most cases, variations present as single nucleotide changes, as in the case of *XPD* and *XRCC-1* genes. In other genes, they can take place as sequence variations or deletions. In many cases, the functional significance of these polymorphisms is unknown. Depending on their location along the gene sequence, polymorphisms may affect gene transcription, translation, mRNA stability, protein activity, or do nothing. Thus analysis of RNA and proteins expressions, using transcriptomic and proteomic technologies, can be envisaged on separated lymphocytes bearing those polymorphisms. In addition, functional studies will increase knowledge on proteins involved in DNA damage repair, and pathways taking place in radiotherapy response. If gene expression or protein activity of these proteins play a critical role in the efficacy or toxicity to a given drug or agent such as radiation, then their respective gene polymorphisms may possess predictive or prognostic value for clinical outcome [Grainger et al, 1999; Andreassen et al, 2002 ; Dikomey et al, 2003]. Moreover, multiple polymorphisms can exist within a single gene, be in linkage disequilibrium, as well as interact with each other.

In contrast, the genetic makeup of tumour cells, which is mainly the result of tobacco smoke induced somatic alterations, is considered important in tumour cell response to radiotherapy. Thus, for the purpose of finding predictive factors of the potential benefit of radiotherapy, we will study tumour cell characteristics using immunohistochemical analysis of protein expression and activation state, and correlate tumour cell data with polymorphisms in germ-line cells.

This project of identifying genes and proteins involved in tumour DNA damage repair, signalling, and ionising radiation resistance among patients enrolled in this randomized trial evaluating post-operative radiotherapy, as well as identifying polymorphisms predictive of disease recurrence after irradiation or predictive of toxicity, would allow biologically based optimisation of treatment intensity in future trials.

22.3.2 Background

Predictive factors of survival benefit or radiation-induced toxicity are likely to be found among proteins that are involved in the molecular mechanisms of cell or tissue response to ionising radiation induced damage. At the cellular level, an important factor of response to ionising radiation is the capacity to repair DNA damage [Jackson, 2002; Willers et al, 2004]. There is also evidence that classical transduction pathways, particularly those downstream of EGFR signalling, crosstalk with DNA repair pathways [Grana et al, 2002; McKenna, 2003; Gupta, 2005]. Radiation-induced lung toxicity is mainly represented by pulmonary fibrosis [Kong et al, 2005].

DNA damage repair

Ionising radiation causes DNA double-strand break (DSB). Cells respond to DSB through the action of systems that can be viewed as transduction cascades : the DNA damage is detected by a sensor that triggers the activation of a protein kinase cascade, which targets a series a downstream systems that slow cell cycle and repair DNA [Jackson, 2002; Willers et al, 2004]. A crucial component of the DSB signalling in mammalian cells is the protein kinase ATM [Pincheira et al, 2001]. While predisposing to human cancer, ATM deficiency, at the cellular level, is related to increased sensitivity to ionising radiation and other agents that yield DSB. Another DNA-damage surveillance protein that is related to ATM is ATR, which plays a particularly important role in signalling DNA damage during S-phase [Cliby et al, 2002]. There are two complementary pathways for DSB repair – homologous recombination (HR) and non-homologous end joining (NHEJ). Their components include : Ku proteins, DNA-PKcs, XRCC4, and ligase IV for NHEJ ; mammalian homologues factors in the yeast ‘RAD50 group’, DNA Pol I, and ligase I for HR. Recent work has established strong links between HR and the breast susceptibility proteins, BRCA1 and BRCA2 as well as the ATM- and ATR-dependent systems.

Radiation and chemotherapy-mediated cell killing of human cancer cells is enhanced by siRNA silencing of DNA repair factors [Collis et al, 2003]. Histone H2AX phosphorylation predicts radio sensitivity of human tumour cell lines and xenografted tumours [Taneja et al, 2004].

It has been reported that polymorphisms or expression levels in tumour cells of XRCC genes have an effect on the survival of lung [Yoon et al, 2005] or other cancer [Moullan et al, 2003 ; De Ruyck et al, 2005 ; Sak et al, 2005] patients treated with radiotherapy.

In a study involving 41 patients using single nucleotide polymorphisms (SNPs) analysis, the SNPs for XRCC3 codon 241 Thr/Met, and the XRCC1 codon 399 Arg/Gln were predictive for the development of radiation-induced grade 3 subcutaneous fibrosis, while only the SNP for XRCC3 codon 241 Thr/Met was predictive for grade 2-3 telangiectasia [Andreassen et al, 2003].

EGFR dependent signalling

Modulation of EGFR pathways can increase the clinical efficacy of radiotherapy in head and neck cancer [Bonner et al, 2006]. Over expression of EGFR either through amplification or mutations has been shown to correlate with a decreased sensitivity to ionising radiation (IR) in preclinical models and to a decreased local control after radiotherapy in lung cancer patients [Harari et al, 2004 ; Gupta et al, 2004]. Hyper activated EGFR activates the MAPK and PI3-kinase AKT signalling cascades. Although MAPK activation is tightly linked to EGFR activation, it has very little contribution to radiation resistance mechanisms [Grana et al, 2002]. Oppositely, PI3-kinase activation directly through interaction with the SH2 domain of receptor tyrosine kinase or indirectly via a Raf-1/Ras dependant pathway is a major contributor of EGFR mediated radiation resistance signalling. Activation of PI3-kinase leads to AKT phosphorylation; activation of AKT has been shown to play a central role in tumour resistance to radiation [Gupta et al, 2002 ; Kim et al, 2004]. AKT activates many pathways, among them is the mTor/HIF-1alpha/VEGF pathway crucial for radiation response to IR [Moeller et al, 2004].

Some polymorphisms in the ERB / Raf-1 / RAS / PI3-+kinase / AKT have been already identified and related to clinical end-points in some cases :

- AKT polymorphisms in have been associated with changes in radiation induced apoptosis in lymphocytes [Harris et al, 2005].
- EGFR polymorphisms have been linked to pelvic recurrence after chemoradiation for rectal cancer [Zhang et al, 2005].

Cytokines and metalloproteinases

Several molecular mechanisms seem to be involved in radiation induced lung damage. First, this fibrosis is a consequence of the process of repair initiated by tissue injury from irradiation. Research in radiation pulmonary injury has supported the involvement of cytokine factors. Cell death caused by irradiation is followed by tissue repair characterised by release of biological mediators like cytokines. Radiation fibrosis develops when a cytokine cascade started by the

cellular injury induced by radiation leads to recruitment of fibroblasts and collagen synthesis. Of the cytokines, TGF-ß has been thought to be one of the most crucial for several years [Burger et al, 1998]. Animal data have shown an early overproduction of pro-inflammatory cytokines such as interleukin-1 (IL-1), tumour necrosis factor-α (TNF- α), and pro-fibrogenic cytokines such as transforming growth factor beta 1 (TGFß-1) during radiotherapy and have suggested a role of the sustained production of these cytokines in the development of acute and late pulmonary toxicities [Rubin et al, 1995]. The process leading to radiation injury is dynamic and involves a number of proinflammatory cytokines, profibrotic cytokines, and chemokines produced by macrophages, fibroblasts and epithelial cells. Chemotactic factors for fibroblasts include transforming growth factor-ß (TGF- ß), fibronectin, and platelet derived growth factor (PDGF) [Abratt et al, 2002 ; Kong et al, 2005]. In breast cancer, TGF-beta 1 polymorphisms have been linked to increased susceptibility to breast cancer [Shin et al, 2005], as well as a higher relapse risk [Skerrett et al, 2005] and to a higher rate of late toxicity after breast irradiation [Andreassen et al, 2005]. The SNPs for the TGFβ1 codon 10 Leu/Pro and for the TGFβ1 position 2509 C/T were shown predictive for the development of grade 3 subcutaneous fibrosis [Andreassen et al, 2003]. The demonstration that the Pro allele in TGFβ1 codon 10 and the T allele in position 2509 correlates with increased risk of radiation-induced subcutaneous fibrosis is of particular importance for PORT, as it is consistent with reports suggesting that the Pro allele in codon 10 increases the circulating level of TGFβ1 [Yamada et al, 1998] and promotes disease progression in patients with idiopathic pulmonary fibrosis [Xaubet et al, 2003]. Furthermore, a recent study described that inhibition of PDGF attenuates pulmonary fibrosis. Other factors have been also reported in the involvement of profibrotic activities like IL-1, bFGF and thrombin [Abdollahi et al, 2005].

In addition, it has been shown that metalloproteinases (MMP), like macrophage elastase (MMP-12) and gelatinases (MMP-2 and MMP-9) are involved in pulmonary fibrosis [Corbel et al, 2002]. MMP are a major group of proteinases known to regulate the remodelling of the lung interstitium extracellular matrix. Indeed, MMP-12 degrades extracellular matrix components such as elastin and is involved in tissue remodelling process. This excessive lung tissue remodelling seems to result from an imbalance in the equilibrium of the normal processes of synthesis and degradation of extracellular components.

Thus it would be of interest to analyse polymorphisms in these different groups of genes implicated in pulmonary fibrosis in order to determine individual genetic background associated with personal radiotherapy sensibility.

22.3.3 Aims

General aim : To identify factors that can predict for the efficacy of radiotherapy and factors that can predict radiation-related toxicity.

Specific aims :

A. Prediction of disease recurrence in patients treated by radiotherapy :
   a. DNA damage repair
      i. Protein expression in tumour cells
      ii. Gene polymorphisms
   b. EGFR dependent pathways
      i. Phosphorylated protein expression in tumour cells
      ii. Gene polymorphisms

B. Prediction of radiation-induced toxicity with gene polymorphisms :
   a. DNA damage repair genes
   b. EGFR pathway genes
   c. Tissue injury, remodelling and fibrotic pathway genes

The current proposal is based on current biological knowledge. As this project will not be performed before 3-4 years, a specific protocol based on the current proposal and taking into account more recent research on this field will be prepared before performing any biological analysis.

22.3.4 Biological material and methods

A. Material :

   a. Tissue samples :
      - One fixed paraffin-embedded sample from each patient will be addressed to Institut Gustave-Roussy ;
      - A central review by a senior pathologist will be performed to confirm diagnosis and assess presence of tumour tissue as well necrosis, inflammation, etc ;
      - Tumour areas will be pointed in order to produce tissue micro arrays (TMA) from the whole collection.

   b. Blood samples :

<u>Blood samples collection</u> :

After having obtained the signed informed consent, 20 ml of venous peripheral blood sample will be taken far from blood transfusion (at least 3 weeks) and before radiotherapy.

- 5 ml venous peripheral blood sample on EDTA
- 15 ml on heparin

The blood sample will be kept at room temperature until the company (DHL) collects it for dispatch (the same day). (Please follow the blood sample collection and dispatch procedure supplied).

- Blood samples will be sent to Institut Gustave-Roussy ;
- Mononuclear cells will be separated according to standard procedure (Ficoll).

B. Methods :

a. Immunohistochemistry :

- Antibodies will be applied to sections after epitope retrieval if needed ;
- Candidate markers are shown below :

Signalling	Phosphorylated-AKT	Cell Signalling Technology
	Phosphorylated ERK	Cell Signalling Technology
	Phosphorylated DNA-PK	Cell Signalling Technology
Chromatin structure	Phosphorylated H2AX	Cell Signalling Technology
HR	RAD 51	Neomarkers
DNA repair	XRCC proteins	ACRIS or Neomarkers
Hypoxia	HIF1alpha	Neomarkers
Cell cycle	Ki67, cyclin B1	Dako or Neomarkers

- Revelation will be performed using Vectastain Elite kit with Novared as substrate and Mayer's haematoxylin as counterstain ;
- Reactivity will be assessed without knowledge of the clinical data using a software for analysis of TMA (Spotbrowser or TMAJ).

b. Analysis of DNA samples

- DNA will be extracted from blood sample according to standard procedure (Qiagen) ;
- Analyses of polymorphisms will be performed using a combination of techniques ; allelic discrimination by quantitative PCR (Taqman) and sequencing of SNP or other gene arrays for selected genes that are involved in DNA damage repair, EGFR signalisation, and inflammation/remodelling/fibrosis.
- Lymphocytes will be separated using a Ficoll method before being cryoconserved in Gustave-Roussy Institute. Immortalisation of lymphocytes will be done (in the Genethon) in order to study RNA or proteins of interesting metabolic pathways.

22.3.5 Choice of endpoint

Considering the rate of death from intercurrent disease (DID), it varies significantly across the studies. In the Dautzenberg study, the rate of DID at 5 years was 8% in the control arm vs 31% in the PORT arm. With more modern radiotherapy techniques, in the more recent Intergroup study, the rate of DID was 12.9% at 4 years not significantly different from the DID expected in the United States considering age, gender and tobacco consumption.

The risk of pneumonitis after PORT is <10% if we consider past trials. According to the ECOG study (E3590) published in 2000, in the PORT arm, the rate of pneumonitis (grade ≥3 according to CTC scale) is less than 2% and treatment-related mortality was 1.2% with a median follow-up of 44 months [Keller et al, NEJM 2000]. Among the 242 patients included in the PORT arm, 22 patients

died of cardio-pulmonary causes (about 50% of each respectively). In the Dautzenberg study, the rate of grade 3 and 4 respiratory toxicities was 4%, and the rate of oesophageal toxicities was 2% [Dautzenberg et al, 1999]. The spectrum of delayed radiation induced heart diseases include pericardial diseases (<10%), myocardial disease, coronary diseases (less frequent) and valve defects or conduction abnormalities. The data we have are mostly issued from Hodgkin or breast series as specified in the chapter toxicity 3.3.2.

To evaluate pulmonary toxicity, patients will have yearly evaluation of pulmonary function. The value of DLCO as well as the value of FEV1 will be collected and analysed in the two groups. Their values will be analysed across time. To evaluate cardiac toxicity, cardiac ultrasound will be performed yearly and we will collect information concerning the resting ejection fraction.

So the methodology for the statistical analysis will be the following :

22.3.6 Methodology of statistical analysis

A. Tumour markers

Three-year disease-free survival will be the main endpoint. The prognostic and predictive role of markers will be studied with a Cox model.

Descriptive analysis

- Distribution of the markers in the study population.
- Determination of the relationship between markers and clinical parameters in particular histology, tumour size, tobacco consumption.
- Determination of the relationship between markers.

Prognostic and predictive analysis

The following strategy of analysis is aimed to limit the number of analyses performed.

Starting model :

As a starting point, the Cox model will include the clinical prognostic factors isolated in the main analysis of Lung-ART, together with the treatment and any significant interaction between treatment and these factors (“the clinical model”). This will be adjusted on the factors used in the randomisation process.

Model for tumor markers :

The first step will be to test the prognostic value of the marker one by one ; then the significant markers (p=0.05) will be entered in the clinical model leading to the final model.

For the predictive analysis, the same strategy will be used, but interaction terms between markers and treatment will be included if significant.

Multiplicity and power issues

The multiplicity problem will be addressed by limiting the number of markers studied with a maximum of 10 (currently 9 are selected) and by using the analysis plan above to limit the number of analyses. Contact with other groups to validate the results on another population will be taken.
The 2 tables below provide examples of power computation for different scenarios. Based on these examples, we can conclude that there will be enough power for the prognostic analysis, but that the project will only allow to detect large difference for the predictive analysis, 20% or more of difference in treatment effect between marker positive and marker negative patients (provided a not too unbalanced number of marker positive and negative patients).

Table 1: Prognostic study : Power variation according to the percentage of marker-positive patients and the expected 3-year disease-free survival difference between marker-positive and marker-negative patients (2 sided test; alpha level 5%), assuming 700 patients.*

Expected survival difference	% of marker-positive patients								
	5%	10%	25%	40%	50%	60%	75%	90%	95%
10%**	27%	46%	76%	86%	87%	86%	76%	46%	27%
20%***	78%	96%	99%	99%	99%	99%	99%	96%	78%

* calculations based on Schmoor C, Sauerbrei W and Schumacher M. Sample size considerations for the evaluation of prognostic factors in survival analysis. Stat Med. 2000 ;19(4):441-452

** 25% 3-year disease-free survival in marker-negative patients vs. 35% in marker-positive patients

*** 20% 3-year disease-free survival in marker-negative patients vs. 40% in marker-positive patients

Table 2 : Predictive study : Power variation according to the percentage of marker positive patients and the expected interaction between radiotherapy and the marker on 3-year disease-free survival (2 sided test; alpha level 5%), assuming 700 patients.*

Expected difference in effect of radiotherapy between marker positive and marker negative patients	% of marker-positive patients								
	5%	10%	25%	40%	50%	60%	75%	90%	95%
10%**	9%	14%	25%	31%	32%	31%	25%	14%	9%
20%***	26%	43%	74%	83%	85%	83%	74%	43%	26%

* calculations based on Schmoor C, Sauerbrei W and Schumacher M. Sample size considerations for the evaluation of prognostic factors in survival analysis. Stat Med. 2000 ;19(4):441-452

** 3-year disease-free survival difference between radiotherapy treated and untreated patients: -5% in marker-negative patients vs. +5% in marker-positive patients

*** 3-year disease-free survival difference between radiotherapy treated and untreated patients: -5% in marker-negative patients vs. +15% in marker-positive patients

B. Gene polymorphisms

The clinical endpoint chosen to study toxicity will be the 3-year rate of intercurrent cardio-pulmonary death, the 3-year rate of pulmonary abnormalities (reduction of respiration volume and/or diffusion capacity) and the 3-year rate of cardiac ultrasound abnormalities (decline of resting ejection fraction).

If the option chosen is to study a limited number of gene polymorphisms (15-20 currently planned), a similar statistical method will be used with a p-value of 0.01 because of the larger number of analyses planned. If a larger number of polymorphisms are studied, other statistical methods will be used. Particular care will be taken to limit the multiplicity problem and to validate the results on another population. Geographical origin will be taken into account in the analysis.

22.4 Randomisation Form

Randomisation form

Centre number ..... ct |___|___|___|___|

Patient-name (3 first letters of last name and 2 first letters of first name) ..... nom |___|___|___| |___|___|

Date of birth (DD,MM,YY) .....datnais |___|___| |___|___| |___|___|

Gender : (**1**=Male, **2**=Female) ..... sex |___|

Performance status (WHO) ..... who|___|

Date of surgery (DD, MM, and YY) .....datsurg1 |___|___| |___|___| |___|___|

Histology (**1**=Squamous cell carcinoma, **2**=Adenocarcinoma, **3**=Large cell carcinoma, **4**=Mixed, **5**=Other) ..... histo |___|

Number of mediastinal nodes stations involved (**0**= None, **1**=One station involved, **2**=Stations involved ≥ 2) ..... nodstat1 |___|

pTNM Stage . ..... pT |___| pN |___| M |___|

Chemotherapy (**0**=No CT, **1**=Preop CT, **2**=Postop CT, **3**=Pre and postop CT) ..... chemo |___|

Date of the last administration of postoperative CT (DD,MM,YY) .....datpoct1 |___|___| |___|___| |___|___|

PET scan before treatment ..... scan ☐ Yes ☐ No

If yes, date (DD,MM,YY) ..... datscan |___|___| |___|___| |___|___|

Inclusion criteria *(cf. criteria list)*

Does the patient satisfy all inclusion criteria (n°1 to 8) ? ..... inclu ☐ Yes ☐ No

Exclusion criteria ***(cf. criteria list)***

Does the patient satisfy all exclusion criteria (n°1 to 13) ? ..... exclu ☐ Yes ☐ No

Translational research

Will the patient take part in the biological study (blood sample) ? ..... blood ☐ Yes ☐ No

Will the patient take part in the biological study (tumour block) ? ..... block ☐ Yes ☐ No

Economic research (for French centers only)

Will the patient take part in the economic study? ..... econ ☐ Yes ☐ No

Date of signature of informed consent (DD,MM,YY).....datcons |___|___| |___|___| |___|___|

Investigator's name : .....Signature :.....

For randomisation please connect to the web site https://fr.tenalea.net/igr/
or : fax this request and the following page to Gisèle Goma +33.(0)1.42.11.52.05
In case of emergency please phone +33.(0)1.42.11.54.72, BEEP : +33.(0)1 42 11 49 00

RANDOMISATION CONFIRMATION

Date of randomisation (DD,MM,YY) ..... datrand |___|___| |___|___| |___|___|

Patient's number ..... numpat |___|___|___|___|

Treatment assigned :

1=no radiotherapy

2=radiotherapy ..... treat |___|

22.5 Acute and late toxicity : CTCAE Scale (Version 3.0)

For further information, please browse on http://ctep.cancer.gov

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)
Publish Date : December 12, 2003

QUICK REFERENCE

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline :

Grade 1 Mild AE
Grade 2 Moderate AE
Grade 3 Severe AE
Grade 4 Life-threatening or disabling AE
Grade 5 Death related to AE

REMARK

A 'REMARK' is a clarification of an AE.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently

		GRADE				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
AUDITORY / EAR						
Tinnitus	Tinnitus	—	Tinnitus not interfering with ADL	Tinnitus interfering with ADL	Disabling	
Auditory/Ear – Other (Specify)	Auditory/Ear – Other (Specify)	Mild	Moderate	Severe	Life-threatening ; disabling	Death
BLOOD/ BONE MARROW						
Bone marrow cellularity	Bone marrow cellularity	Mildly hypocellular or ≤25% reduction from normal cellularity for age	Moderately hypocellular or >25 – ≤50% reduction from normal cellularity for age	Severely hypocellular or >50 – ≤75% reduction cellularity from normal for age	—	Death
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 gldL <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/mm^3 <LLN – 3.0x10^9/L	<3000–2000/mm^3 <3.0 – 2.0x10^9/L	<2000–1000/mm^3 <2.0 – 1.0x10^9/L	<1000/mm^3 <1.0x10^9/L	Death
Lymphopenia	Lymphopenia	<LLN – 800/mm^3 <LLN x0.8–10^9/L	<800– 500/mm^3 <0.8–0.5x10^9/L	<500 – 200 mm^3 <0.5 – 0.2x10^9/L	<200/mm^3 <0.2x10^9/L	Death
Neutrophils/Granulocytes (ANC/AGC)	Neutrophils	<LLN – 1500/mm^3 <LLN – 1.5 x 10^9 /L	<1500 – 1000/mm^3 <1.5 – 1.0 x 10^9 /L	<1000 – 500/mm^3 <1.0 – 0.5 x 10^9 /L	<500/mm^3 <0.5 x 10^9 /L	Death
Platelets	Platelets	<LLN – 75,000/mm^3 <LLN – 75 0 x 10^9 /L	<75,000 – 50,000/mm^3 <75.0–50.0x10^9 /L	<50,000 – 25,000/mm^3 <50.0 – 25.0x10^9/L	<25,000/mm^3 <25.0 x 10^9 /L	Death
Blood/Bone Marrow – Other (Specify)	Blood – Other (Specify)	Mild	Moderate	Severe	Life-threatening ;disabling	Death

CARDIAC ARRHYTHMIA						
Palpitations	Palpitations	Present	Present with associated symptoms (e.g., lightheadedness, shortness of breath)	—	—	—
REMARK : Grade palpitations only in the absence of a documented arrhythmia.						
Supraventricular and nodal arrhythmia	Supraventricular arrhythmia –	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Select – Atrial fibrillation – Atrial flutter – Atrial tachycardia/Paroxysmal Atrial Tachycardia – Nodal/Junctional – Sinus arrhythmia – Sinus bradycardia – Sinus tachycardia – Supraventricular arrhythmia NOS – Supraventricular extrasystoles (Premature Atrial Contractions; Premature Nodal/Junctional Contractions) – Supraventricular tachycardia						
Vasovagal episode	Vasovagal episode	—	Present without loss of consciousness	Present with loss of consciousness	Life-threatening consequences	Death
Cardiac Arrhythmia– Other (Specify,_)	Cardiac Arrhythmia – Other (Specify,_)	Mild	Moderate	Severe	Life-threatening; disabling	Death
CARDIAC GENERAL						
Cardiac ischemia/infarction	Cardiac ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	Death
Cardiopulmonary arrest, cause unknown (non-fatal)	Cardiopulmonary arrest	—	—	—	Life-threatening	—
REMARK: Grade 4 (non-fatal) is the only appropriate grade. CTCAE provides three alternatives for reporting Death: 1. A CTCAE term associated with Grade 5. 2. A CTCAE 'Other (Specify)', within any CATEGORY. 3. Death not associated with CTCAE term – *Select* in the DEATH CATEGORY.						
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated	Recurrent or persistent (>24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously	Life-threatening consequences (e.g., hypertensive crisis)	Death
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (>24hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)	Death

Left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40%; SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
Pericardial effusion (non-malignant)	Pericardial effusion	Asymptomatic effusion	—	Effusion with physiologic consequences	Life-threatening consequences (e.g., tamponade); emergency intervention indicated	Death
Pericarditis	Pericarditis	Asymptomatic, ECG or physical exam (rub) changes consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; emergency intervention indicated	Death
Cardiac General – Other (Specify, _)	Cardiac General – Other (Specify, _)	Mild	Moderate	Severe	Life-threatening; disabling	Death
CONSTITUTIONAL SYMPTOMS						
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 neutropaenia, where neutropaenia is defined as ANC <1.0 x 10^9/L)	Fever	38.0 — 39.0℃	>39.0 — 40.0℃	>40.0℃ for <24hrs	>40.0℃ for >24hrs	Death
REMARK: The temperature measurements listed are oral or tympanic.						
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.						
Sweating (diaphoresis)	Sweating	Mild and occasional	Frequent or drenching	—	—	—
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.						
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	—	—
Constitutional Symptoms – Other (Specify)	Constitutional Symptoms – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

DERMATOLOGY/SKIN						
Cheilitis	Cheilitis	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	—	—
Dry skin	Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—
Flushing	Flushing	Asymptomatic	Symptomatic	—	—	—
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	—	—
Nail changes	Nail changes	Discoloration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	—	—
NAVIGATION NOTE : Petechiae is graded as Petechiae/purpura (hemorrhage/bleeding into skin or mucosa) in the HEMORRHAGE/BLEEDING CATEGORY						
Photosensitivity	Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death
Pruritus/itching	Pruritus	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
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 : acne/acneiform	Acne	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Erythema multiforme	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated	Life-threatening; disabling	Death
Urticaria (hives, welts, wheals)	Urticaria	Intervention not indicated	Intervention indicated for <24 hrs	Intervention indicated for ≥24 hrs	—	—
Dermatology/Skin – Other	Dermatology – Other Mild	Moderate	Severe	Life-threatening; disabling	Death	

ENDOCRINE						
Hot flashes/flushes	Hot flashes	Mild	Moderate	Interfering with ADL	—	—
Endocrine - Other (Specify', _)	Endocrine – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death
GASTROINTESTINAL						
NAVIGATION NOTE : Abdominal pain or cramping is graded as Pain – *Select* in the PAIN CATEGORY.						
Abdominal Pain	Abdominal Pain	Mild	Moderate	Severe	—	—
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
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
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; constipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
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
Diarrhoea	Diarrhoea	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 : Diarrhoea includes diarrhoea of small bowel or colonic origin, and/or ostomy diarrhoea.						
Distension/bloating abdominal	Distension	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic, interfering with GI function	—	—

Dry mouth/salivary gland (xerostomia)	Dry mouth	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	—	—
REMARK : Dry mouth/salivary gland (xerostomia) includes descriptions of grade using both subjective and objective assessment parameters. Record this event consistently throughout a patient's participation on study. If salivary flow measurements are used for initial assessment, subsequent assessments must use salivary flow.						
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
Heartburn/ dyspepsia	Heartburn	Mild	Moderate	Severe	—	—
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: Ilieus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying).						
Mucositis/stomatitis (clinical exam) Select : — Anus — Esophagus — Large bowel — Larynx — Oral cavity — Pharynx — Rectum — Small bowel — Stomach — Trachea	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 : — Anus — Esophagus — Large bowel — Larynx — Oral cavity — Pharynx — Rectum — Small bowel — Stomach — Trachea	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 Vomiting.	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
Obstruction, GI *Select :* – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Obstruction, GI – Select	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhoea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, vomiting, diarrhoea, 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
Taste alteration (dysgeusia)	Taste alteration	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	—	—	—
Ulcer, GI Select. – Anus – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Ulcer, GI – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
Gastrointestinal – Other (Specify,)	GI – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death
HEMORRHAGE/BLEEDING						
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
REMARK : Hematoma refers to extravasation at wound or operative site or secondary to other intervention. Transfusion implies pRBC.						
Hemorrhage, CNS	CNS hemorrhage	Asymptomatic, radiographic findings only	Medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; neurologic deficit or disability	Death

Hemorrhage, GI *Select.* – Abdomen NOS – Anus – Biliary tree – Cecum/appendix – Colon – Duodenum – Esophagus – Ileum – Jejunum – Liver – Lower GI NOS – Oral cavity – Pancreas – Peritoneal cavity – Rectum – Stoma – Stomach – Upper GI NOS – Varices (oesophageal) – Varices (rectal)	Haemorrhage, 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.						
Hemorrhage, pulmonary/ upper respiratory – Nose	Hemorrhage pulmonary – *Select*	Mild, intervention not indicated	Symptomatic and medical intervention 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.						
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	Petechiae	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura	—	—
NAVIGATION NOTE : Vitreous hemorrhage is graded in the OCULAR/VISUAL CATEGORY						
Hemorrhage/ Bleeding – Other (Specify,_)	Hemorrhage – Other (Specify,_)	Mild without transfusion	—	Transfusion indicated	Catastrophic bleeding, requiring major non-elective intervention	Death
HEPATOBILIARY/PANCREAS						
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						
Pancreatitis	Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)	Death
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

Hepatobiliary /Pancreas –Other (Specify,)	Hepatobiliary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death
INFECTION						
Colitis, infectious (e.g., Clostridium difficile)	Colitis, infectious	Asymptomatic, pathologic or radiographic findings only	Abdominal pain with mucus and/or blood in stool	IV antibiotics or TPN indicated	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis or toxic megacolon); operative resection or diversion indicated	Death
Febrile neutropaenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C)	Febrile neutropaenia	—	—	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select*	Infection (documented clinically) – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK : Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropaenia (fever of unknown origin without clinically or microbiologically documented infection).						
Infection with normal ANC or Grade 1 or 2 neutrophils – Select	Infection with normal ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
Infection with unknown ANC – *Select* Se/ect'AEs appear at the end of the CATEGORY.	Infection with unknown ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Infection with unknown ANC – *Select* is to be used in the rare case when ANC is unknown.						
Opportunistic infection associated with ≥Grade 2 Lymphopenia	Opportunistic infection	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death

Viral hepatitis	Viral hepatitis	Present ; transaminases and liver function normal	Transaminases abnormal, liver function normal	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
REMARK : Non-viral hepatitis is graded as Infection – Select.						
Infection – Other (Specify)	Infection – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death
LYMPHATICS						
Dermal change lymphedema, phlebolymphedema	Dermal change	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation	—	—	—
REMARK : Dermal change lymphedema, phlebolymphedema refers to changes due to venous stasis.						
Edema : head and neck	Edema : head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death
Edema : limb	Edema : limb	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour, interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death
Edema : trunk/genital	Edema : trunk/genital	Swelling or obscuration of anatomic architecture on close inspection; pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL; gross deviation from normal anatomic contour	Progression to malignancy (i.e., lymphangiosarcoma); disabling	Death
Edema : viscera	Edema : viscera	Asymptomatic ; clinical or radiographic findings only	Symptomatic ; intervention indicated	Symptomatic and unable to aliment adequately orally; interventional radiology or operative intervention indicated	Life threatening consequences	Death
Lymphatics – Other (Specify,_)	Lymphatics – Other (Specify,_)	Mild	Moderate	Severe	Life-threatening; disabling	Death
METABOLIC/ LABORATORY						
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.						
Calcium, serum-low (hypocalcemia) Ionized calcium :	Hypocalcemia	<LLN - 8.0 mg/dL <LLN - 2.0 mmol/L <LLN - 1.0 mmol/L	<8.0 - 7.0 mg/dL <2.0 - 1.75 mmol/L <1.0 - 0.9 mmol/L	<7.0 - 6.0 mg/dL <1.75 - 1.5 mmo/L <0.9 - 0.8 mmol/L	<6.0 mg/dL <1.5 mmol/L <0.8 mmol/L	Death
REMARK : Calcium tan be falsely low if hypoalbuminemia is present. Serum albumin is <4.0 g/dL, hypocalcemia is reported after the following corrective calculation has been performed: Corrected Calcium (mg/dL) = Total Calcium (mg/dL) - 0.8 [Albumin (g/dL) - 4]. Alternatively, direct measurement of ionized calcium is the definitive method to diagnose metabolically relevant alterations in serum calcium.						
Calcium, serum-high (hypercalcemia) Ionized calcium:	Hypercalcemia	>ULN - 1t5 mg/dL >ULN - 2.9 mmol/L >ULN - 1.5 mmol/L	>11.5 - 12.5 mg/dL >2.9 - 3.1 mmo/L >1.5 - 1.6 mmol/L	>12.5 - 13.5 mg/dL >3.1 - 3.4 mmol/L >1.6 - 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L >1.8 mmol/L	Death
Cholesterol, serum-high (hypercholesterem)	Cholesterol	>ULN - 300 mg/dL >ULN - 7.75mmo/L	>300 - 400 mg/dL >7.75 - 10.34 mmol/L	>400 - 500 mg/dL >10.34 - 12.92mmol/L	>500 mg/dL >12.92 mmol/L	Death
CPK (creatine phosphokinase)	CPK	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	Death
Creatinine	Creatinine	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN	Death
Phosphate, serum-low (hypophosphatemi)	Hypophosphatemia	<LLN - 2.5 mg/dL <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL <0.6 - 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L	Death
Glomerular filtration rate ALSO CONSIDER: Creatinine.	GFR	<75 - 50% LLN	<50 - 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renaltransplant indicated	Death
Potassium, serum-high (hyperkalemia)	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L	Death
Potassium, serum-low (hypokalemia)	Hypokalemia	<LLN – 3.0 mmol/L	—	<3.0 – 2.5 mmol/L	<2.5 mmol/L	Death
Sodium, serum-low (hyponatremia)	Hyponatremia	<LLN – 130 mmol/L	—	<130 – 120 mmol/L	<120 mmol/L	Death
Triglyceride, serum-high (hypertriglyceri-demia)	Hypertriglyceride mia	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN	Death
Uric acid, serum-high (hyperuricemia)	Hyperuricemia	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	—	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L	Death
Metabolic/Laborat ory –Other (Specify)	Metabolic/Lab – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

MUSCULOSKELETAL/SOFT TISSUE						
Joint-effusion	Joint-effusion	Asymptomatic, clinical or radiographic findings only	Symptomatic; interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death
Joint-function	Joint-function	Stiffness interfering with athletic activity; ≤25% loss of range of motion (ROM)	Stiffness interfering with function but not interfering with ADL; >25 – 50% decrease in ROM	Stiffness interfering with ADL; >50 – 75% decrease in ROM	Fixed or non-functional joint (arthrodesis); >75% decrease in ROM	—
Musculoskeletal/ Soft Tissue — Other (Specify)	Musculoskeletal — Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death
Myalgia	Myalgia	Mild	Moderate	Severe	Disabling	—
NEUROLOGY						
Cognitive disturbance	Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability ; interfering with work/school/life performance but capable of independent living ; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	Unable to perform ADL ; full-time specialized resources or institutionalization indicated	Death
REMARK : Cognitive disturbance may be used for Attention Deficit Disorder (ADD).						
Confusion	Confusion	Transient confusion, disorientation, or attention deficit	Confusion, disorientation, or attention deficit interfering with function, but not interfering with ADL	Confusion or delirium interfering with ADL	Harmful to others or self; hospitalization indicated	Death
REMARK : Attention Deficit Disorder (ADD) is graded as Cognitive disturbance.						
Dizziness	Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabling	Death
REMARK : Dizziness includes disequilibrium, lightheadedness, and vertigo.						
Memory impairment	Memory impairment	Memory impairment not interfering with function	Memory impairment interfering with function, but not interfering with ADL	Memory impairment interfering with ADL	Amnesia	—
Mood alteration – *Select* – Agitation – Anxiety – Depression – Euphoria	Mood alteration – *Select*	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or others	Death
Neuropathy : cranial – Select	Neuropathy : cranial	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling	Death

– CN I Smell – CN II Vision – CN III Pupil, upper eyelid, extra ocular movements – CN IV Downward, inward movement of eye – CN V Motor- jaw muscles; Sensory-facial – CN VI Lateral deviation of eye – CN VII Motor-face; Sensory-taste – CN VIII Hearing and balance – CN IX Motor-pharynx; Sensory-ear, pharynx, tongue – CN X Motor-palate; pharynx, larynx – CN XI Motor-stemomastoid and trapezius – CN XII Motor-tongue						
Neuropathy : motor	Neuropathy-motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death
Neuropathy : sensory	Neuropathy-sensory	Asymptomatic ; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
REMARK : Cranial nerve sensory neuropathy is graded as Neuropathy: cranial – *Select.*						
Seizure	Seizure	—	One brief generalized seizure; seizure(s) wellcontrolled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death
Somnolence/ depressed level of consciousness	Somnolence	—	Somnolence or sedation interfering with function, but-not interfering-with ADL	Obtundation or stupor; difficult to arouse; interfering with-ADL	Coma	Death
Syncope (fainting)	Syncope (fainting)	—	—	Present	Life-threatening consequences	Death
NAVIGATION NOTE : Taste alteration (CN VII, IX) is graded as Taste alteration (dysgeusia) in the GASTROINTESTINAL CATEGORY.						
Neurology - Other (Specify,)	Neurology - Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

OCULAR/VISUAL						
Dry eye syndrome	Dry eye	Mild, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL; medical intervention indicated	Symptomatic or decrease in visual acuity interfering with ADL; operative intervention indicated	—	—
Ocular surface disease	Ocular surface disease	Asymptomatic or minimally symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL, topical antibiotics or other topical intervention indicated		—	—
REMARK : Ocular surface disease indudes conjunctivitis, keratoconjunctivitis sicca, chemosis, keratinization, and palpebral conjunctival epithelial metaplasia.						
Optic disc edema	Optic disc edema	Asymptomatic	Decreased visual acuity (20/40 or better) ; visual field defect present	Decreased visual acuity (worse than 20/40) ; marked visual field defect but sparing the central 20 degrees	Blindness (20/200 or worse)	—
Vision-blurred vision	Blurred vision	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vitreous hemorrhage	Vitreous hemorrhage	Asymptomatic, clinical findings only	Symptomatic, interfering with function, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; vitrectomy indicated	—	—
Watery eye (epiphora, tearing)	Watery eye	Symptomatic, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	—	—
Ocular/Visual – Other (Specify)	Ocular – Other (Specify)	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Blindness (20/200 or worse)	Death
PULMONARY/UPPER RESPIRATORY						
Cough	Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	—	—
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 (0.1 km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ ventilator 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

Pneumonitis/ pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; 0_2 indicated	Life-threatening ; ventilatory support indicated	Death
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 dfficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy.						
Pulmonary/Upper Respiratory – Other (Specify)	Pulmonary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death
RENAL/GENITOURINARY						
Renal failure	Renal failure	—	—	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
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	—	—
Renal/ Genitourinary – Other (Specify,)	Renal – Other (Specify)	Mild	Moderate	Severe	Life-threatening ; disabling	Death
SEXUAL/REPRODUCTIVE FUNCTION						
Breast volume/hypoplasia	Breast	Minimal asymmetry ; minimal hypoplasia	Asymmetry exists, ≤1/3 of the breast volume ; moderate hypoplasia	Asymmetry exists, >1/3 of the breast volume ; severe hypoplasia	—	—
REMARK : Breast volume is referenced with both arms straight overhead.						
Erectile dysfunction	Erectile dysfunction	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not indicated	Decrease in erectile function (frequency/rigidity of erections), erectile aids indicated	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	—	—
Ejaculatory dysfunction	Ejaculatory dysfunction	Diminished ejaculation	Anejaculation or retrograde ejaculation	—	—	—
Endometrial hyperplasia	Endometrial hyperplasia	Mild	Moderate	Severe	Life-threatening ; disabling	Death
Gynecomastia	Gynecomastia	—	Asymptomatic breast enlargement	Symptomatic breast enlargement; intervention indicated	—	—
Infertility/sterility	Infertility/sterility	—	Male : oligospermial/low sperm count Female : diminished fertility/ ovulation	Male :sterile/azoospermia Female : infertile/ anovulatory	—	—

Irregular menses (change from baseline)	Irregular menses	1 – 3 months without menses	>3 – 6 months without menses but continuing menstrual cycles	Persistent amenorrhea for >6 months	—	—
Libido	Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	—	—	—
Orgasmic dysfunction	Orgasmic function	Transient decrease	Decrease in orgasmic response requiring intervention	Complete inability of orgasmic response; not responding to intervention	—	—
Sexual/Reproductive Function – Other (Specify,)	Sexual – Other (Specify)	Mild	Moderate	Severe	Disabling	Death
Vaginal discharge (non-infectious)	Vaginal discharge	Mild	Moderate to heavy; pad use indicated	—	—	—
VASCULAR						
Phlebitis (including superficial thrombosis)	Phlebitis	—	Present			Death
Thrombosis/ thrombus/ embolism	Thrombosis/ thrombus/ embolism	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including Pulmonary embolism or life threatening thrombus	Death
Vascular – Other (Specify,)	Vascular – Other (Specify)	Mild	Moderate	Severe	Life-threatening ; disabling	Death

ADL : Activities of Daily Living
ANC : Absolute Neutrophil Count
AGC : Absolute Granulocyte Count
BSA : Body Surface Area
CHF : Congestive Heart Failure
GVHD : Graft-versus-Host-Disease
ICP : Intracranial Pressure
TPN : Total Parenteral Nutrition

22.6 Serious Adverse Events Form

EUDRACT N°: Not applicable	Sponsor's N° : 2006/1202	Country :
☐ Expected serious adverse event	☐ Unexpected serious adverse event	
☐ 1st report	☐ Follow-up report N° |__|	Center : .....

1. PATIENT IDENTIFICATION

Patient Inclusion N° : |_____|	Last Name (3 letters) : |__|__|__|	1st Name (2 letters) : |__|__|	Date of birth : |__|__| / |__|__| / |__|__|__|__|
Gender : ☐ F ☐ M	Weight (kg) : |_____|	Height (cm) : |_____|	Treatment arm: |____|

2. EVENT INFORMATION

Date of onset : \|__\|__\| / \|__\|__\| / \|__\|__\| **NCI – CTCAE V3 grading toxicity: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5**

Diagnosis or main symptom(s) :... .....

.....

3. NARRATIVE

.....

.....

.....

4. THIS SERIOUS ADVERSE EVENT IS DEFINED AS : (please tick √ all boxes that apply)

☐ Death..... date \|__\|__\| / \|__\|__\| / \|__\|__\|

☐ Life threatening

☐ Requiring or prolonging patient's hospitalization: date \|__\|__\| / \|__\|__\| / \|__\|__\|

☐ Medically significant, specify below: .....

☐ Persistent or significant incapacity/disability

☐ Other cancer: .....

☐ Congenital disorder / birth defect

5. SUSPECTED TREATMENTS *(filling the cases, page 2/2)*

6. RELEVANT MEDICAL HISTORY AND/OR CONCOMITANT DISEASES

.....

.....

7. CONCOMITANT MEDICATION

Treatment	Dose/Unit	Route	Indication	First dose	Last dose	Ongoing	Cause/effect relationship		
							yes	no	possible
				|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	☐	☐	☐	☐
				|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	☐	☐	☐	☐
				|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	☐	☐	☐	☐

8. ADVERSE EVENT TREATMENTS

Treatment	Dose/Unit	Route	Indication	First dose	Last dose	Ongoing
				|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	☐
				|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	☐
				|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	☐
				|__|__| / |__|__| / |__|__|	|__|__| / |__|__| / |__|__|	☐

9. OUTCOME

☐ ongoing

☐ Recovered without after-effects date \|__\|__\| / \|__\|__\| / \|__\|__\|

☐ Recovered with after-effects date \|__\|__\| / \|__\|__\| / \|__\|__\|

Nature of after-effects :

... .

☐ Death due to the side effect date \|__\|__\| / \|__\|__\| / \|__\|__\|

☐ Death unconnected with the side effect date \|__\|__\| / \|__\|__\| / \|__\|__\|

☐ Unknown

Date end of the hospitalization : \|__\|__\| / \|__\|__\| / \|__\|__\|

5. SUSPECTED TREATMENTS

CYCLE N° :   DATE FIRST CYCLE : |__|__||__|__||__|__|

	ROUTE	DATES		Dose / unit		TREATMENT MODIFICATIONS			TREATMENTS		
		Most recent administration before SAE		Last dose	cumulative Dose since the 1st administration	(1) No change (2) Delayed (3) Discontinued (4) Dose reduction (5) reduction of infusion rate	if discontinued date of discontinuation	If delayed, stop and restart dates	Did the SAE abate after stopping the treatment 1 : Yes 2 : No 3 : NA	Did the SAE reappear after drug reintroduction 1 : Yes 2 : No 3 : NA	Assessment : 1 : Not related 2 : Unlikely 3 : Possible 4 : Likely 5 : very likely 6 : insufficient data
		From |__|__||__|__||__|__|	To* |__|__||__|__||__|__|	|__|__|__|__|	|__|__|__|__|	|__| If dose reduction, new dose :	|__|__||__|__||__|__|	|__|__||__|__||__|__| |__|__||__|__||__|__|	|__|	|__|	|__|
		From|__|__||__|__||__|__|	To* |__|__||__|__||__|__|	|__|__|__|__|	|__|__|__|__|	|__| If dose reduction, new dose :	|__|__||__|__||__|__|	|__|__||__|__||__|__| |__|__||__|__||__|__|	|__|	|__|	|__|
		From|__|__||__|__||__|__|	To* |__|__||__|__||__|__|	|__|__|__|__|	|__|__|__|__|	|__| If dose reduction, new dose :	|__|__||__|__||__|__|	|__|__||__|__||__|__| |__|__||__|__||__|__|	|__|	|__|	|__|
		From|__|__||__|__||__|__|	To* |__|__||__|__||__|__|	|__|__|__|__|	|__|__|__|__|	|__| If dose reduction, new dose :	|__|__||__|__||__|__|	|__|__||__|__||__|__| |__|__||__|__||__|__|	|__|	|__|	|__|

*At onset of the SAE, if treatment is continuing, enter "Cont" under date-to

10. Assessment *(According to you, the SAE is more likely due to)*

- ☐ Evaluated treatment(s) (which one)..
- ☐ Disease progression
- ☐ Trial protocol
- ☐ Other concomitant disease(s), pre-existing condition, specify...............
- ☐ Other concomitant treatment(s), specify...
- ☐ Other (including underlying malignancy) :specify..

11. Reporter

Name and position of the reporter :

Name :
Adress:
Phone :
Fax :
E-mail :

Date |__|__| / |__|__| / |__|__|

Signature of the investigator / co-investigator

22.7 Performance Status (WHO)

ECOG PERFORMANCE STATUS	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

22.8 Economics Study

For French centres or other centres who might be interested.

Writing Committee: A. Aupérin, J. Bonastre.

22.8.1 Overview

A cost-effectiveness analysis will be performed to assess the cost of an additional year free of disease obtained by conformal thoracic radiotherapy as compared to no radiotherapy. Effectiveness (i.e. number of years free of disease) will be estimated by the difference of disease free survival means between the two arms for all the patients in the trial. Costs will be estimated for France only. Costs incurred by payer will be considered: medical costs after randomisation during treatment and follow-up, travel costs supported reimbursed by sickness funds. Resources will be measured during a three-year period after randomisation or until local or regional recurrence if relapse occurs. Only costs differing between the two arms will be considered.

22.8.2 Use of resources

Patient specific data will be collected in the two arms:

- **During radiotherapy for the RT arm**

The cost of radiotherapy has three components: dosimetry, irradiation and surveillance. Irradiation (number of fractions) and dosimetry will be valued using the mean cost of appropriate diagnosis related group. Information on inpatient stays for toxicities during the irradiation will be collected (length of stay and type of unit).
The estimation of hospital travel costs supported by sickness funds (e.g. ambulance) will be based on :

- the distance between patient's home and the centre where the irradiation is performed
- and the type of transportation most frequently used during RT.

- **After treatment (RT for the RT arm and surgery or post-operative chemotherapy for the no RT arm)**

Between the end of treatment to the diagnosis of recurrence, inpatient stays (including emergency care visits and home care) for late toxicities or complications or for suspicion of a recurrence or for any reason related to lung cancer will be collected in the case report form.
Patient self-report will be used to collect medical resources use for all outpatient (visits, and major radiologic tests and sick leaves). Medical resource use outside the centre : inpatient stays, major radiologic investigations[1], visits to specialists related to lung cancer or adverse events during a three-year period or to recurrence if the patient relapses before, will also be collected.

22.8.3 Costing methodology

Inpatient stays and outpatient resources will be valued using respectively French diagnosis related groups and official tariffs.

22.8.4 Analysis

The difference of costs between the two arms will be tested using the Wilcoxon statistic. Cost drivers will be searched using linear regression models. If the disease free survival is higher with RT, the incremental cost effectiveness ratio will be calculated. It represents the cost per year of added disease-free survival. A 95% confidence interval of the incremental cost effectiveness ratio will be produced using the non-parametric bootstrap method.

[1] Major investigations include pulmonary radiography, chest CT-scan, pulmonary MRI, PETscan, bronchial fibroscopy, cardiac ultra-sound, myocardial scintigraphy, cardiac functional testing, lung function tests, gastro-oesophagus fibroscopy, abdominal CT-scan, cerebral MRI.