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Director: Prof. **Giuseppe Biagini**

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The use of statistical methods in clinical research

Candidate **Shaniko Kaleci**

Tutor: Prof. **Roberto D'Amico**

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Summary

The research activities I have carried out in the most recent years have been centered on the methodology of statistical analyses in clinical research. One of these activities have been centered on the methodology of randomized controlled clinical trials. In particular I followed the IRMA trial, which international an randomized controlled trial aimed at comparing partial and accelerated irradiation with three-dimensional conformal radiotherapy (3D-CRT) vs. standard radiotherapy in women suffering from breast cancer with low risk of local recurrence and undergoing conservative surgery.

The acronym IRMA stands for "Breast cancer with low risk of local recurrence: partial and accelerated irradiation with three-dimensional conformal radiotherapy (3D-CRT) vs. standard radiotherapy after conserving surgery (phase III study)".

This study has been active in Emilia - Romagna starting since 2007.

Patient recruitment has been carried out by evaluating the inclusion criteria and by administering informed consent. Randomization has been performed stratifying for three factors:

1. lymph nodes (N0 and N1);

2. T dimension (T1 and T2);

3. chemotherapy treatment (Yes, No).

The primary objective of the research is to evaluate whether partial hypofractionated and accelerated irradiation of the sole surgical cavity in patients with breast cancer at low risk of local recurrence undergoing conservative surgery, is not inferior to postoperative irradiation with conventional fractionation of the entire breast with regard to the local control,measured in terms of incidence of ipsilateral recurrences as the first event.

The survey, globally considered, was essentially with two main aims:

- To make a comparison of the overall survival rates, free of local/loco-regional recurrences and time-distant relapses, in patients treated with conventional radiotherapy and accelerated partial irradiation.

- To assess whether the accelerated partial irradiation provides best cosmetic results, possibly reducing the acute toxicity grade, in comparison with conventional irradiation.

Actually, the possibility of limiting radiation therapy just to the lumpectomy cavity and its surrounding tissues, could allow to achieve the following goals:

- A drastic reduction in the duration of radiotherapy;

- A local disease control comparable to that of conventional treatment;

- A less toxicity grade at the level of organs at risk (OAR) and cutaneous and subcutaneous tissues;

- A better acceptability and adherence of patients to treatment;

- A reduction of the clinical cases with non-optimal treatments (mastectomies applied to patients candidates to conservative surgery, breast-conserving surgery not followed by radiation therapy, etc.).

The present study will deal with the following topics:

- Definition of randomized controlled trials and statistical analysis of such trials;

- Description of the Protocol of IRMA trial;

- Statistical analysis of the results of IRMA - trial;

- prevalence and diagnosis of vestibular disorders in children, a review of the literature;

- incidence of clinical features of colorectal cancer patients in advanced age;

- the EUROCARE high resolution study of disease presentation, treatment and survival for Italian colorectal cancer patients;

- study of preoperative predictions of successful surgical treatment in the management of parapneumonic empyema;

Riassunto

L'attività di ricerca svolta in questi anni si è focalizzata sulla metodologia dell'analisi statistica applicata alla ricerca clinica. Una di queste attività riguarda la metodologia degli studi clinici controllati e randomizzati. In particolare ho seguito lo studio IRMA, che è uno studio internazionale finalizzato al confronto dell'irradiazione parziale e accelerata con radioterapia conformazionale tridimensionale (3D-CRT) vs. radioterapia standard nelle donne affette da cancro al seno a basso rischio di recidiva locale in chirurgia conservativa.

L'acronimo IRMA è "carcinoma della mammella a basso rischio di recidiva locale: irradiazione parziale e accelerata con radioterapia conformazionale tridimensionale (3d-crt) vs. radioterapia standard dopo chirurgia conservativa (studio di fase III)".

Questo studio si è attivato in Regione Emilia – Romagna a partire al 2007.

L'arruolamento dei pazienti è svolta mediante valutazione dei criteri di inclusione e somministrazione diretta del consenso informato e la randomizzazione viene effettuata stratificando per tre fattori:

1. linfonodi (N0 e N1);

2. dimensione di T (T1 e T2);

3. trattamento chemioterapia (Si, No).

Obiettivo primario della ricerca è di valutare se l'irradiazione parziale ipofrazionata ed accelerata della sola cavità chirurgica, nelle pazienti affette da carcinoma della mammella a basso rischio di ricaduta locale sottoposte a chirurgia conservativa, non è inferiore all'irradiazione postoperatoria con frazionamento convenzionale dell'intera mammella per quanto riguarda il controllo locale (incidenza di recidive ipsilaterali come primo evento).

L'indagine, nel suo complesso, è svolta a confrontare le sopravvivenze globali, libere da recidive locali e locoregionali , libere da ricadute a distanza nelle pazienti trattate con radioterapia convenzionale e irradiazione parziale accelerata.

Valutare se l'irradiazione parziale accelerata offre risultati cosmetici, tossicità acute comparabili rispetto all'irradiazione convenzionale.

Limitare il trattamento radioterapico alla cavità della tumorectomia ed alle sue adiacenze, potrebbe permettere di ottenere:

- Una drastica riduzione della durata della radioterapia; Un controllo locale della malattia paragonabile a quello del trattamento convenzionale;
- Una minor tossicità a livello degli organi a rischio (OAR) e dei tessuti cutanei e sottocutanei;
- Una migliore accettabilità ed adesione delle pazienti al trattamento:
- Una riduzione dei trattamenti locali non ottimali (mastectomie in pazienti candidate a chirurgia conservativa, chirurgia conservativa non seguita da radioterapia).

Nella presente tesi verranno trattati gli seguenti argomenti:

- Definizione dei studi clinici randomizzati e controllati e l'analisi statistica di questi studi;
- Il protocollo del IRMA trial;
- I risultati dello studio clinico randomizzato e controllato -IRMA;
- studio di prevalenza e la diagnosi di disturbi vestibolari nei bambini, una revisione della letteratura;

- incidenza delle caratteristiche cliniche dei pazienti affetti da cancro del colon-retto in età avanzata;

- lo studio alta risoluzione EUROCARE, presentazione della malattia, il trattamento e la sopravvivenza nei pazienti affetti da cancro del colon-retto italiani.

- studio delle previsioni preoperatorie del trattamento chirurgico di successo nella gestione di empiema parapneumonico

Chapter 1

Methodology for the management and analysis of studies assessing efficacy and safety of health care interventions: IRMA trial

1.1 Abstract

Background: Whole-breast radiotherapy after conservative surgery in women with early breast cancer is a routine standard of care. Over recent years, a number of new technologies have allowed the development of partial-breast irradiation, with the intention of improving the risk-benefit relationship of breast radiotherapy, in terms of lower toxicity, best cosmetic result and best compliance.

Objectives: The primary objective is to evaluate whether partial hypofractionated and accelerated irradiation of the sole surgical cavity is not inferior to postoperative irradiation with conventional fractionation of the entire breast as regards local control, measured in terms of incidence of ipsilateral recurrences as the first event. Secondary objectives are to compare the two methods of irradiation in terms of: a) overall survival; b) locoregional recurrence free survival; c) distant relapse-free survival (except for local or regional relapses or in the contralateral breast); d) cosmetic results; e) acute toxicity.

Methods: IRMA is a randomized controlled trial aimed at comparing partial and accelerated radiation with three-dimensional conformal radiotherapy (3DCRT) vs. standard radiotherapy in women aged $\geqq$ 49, ECOG 0-2, undergoing conserva-

tive breast surgery for invasive breast cancer, pT 1-2 (< 3 cm in diameter) pN0-N1 M0, unifocal, histologically negative resection margins ($\geq$ 2 mm) at first intervention or after subsequent widening. In the experimental arm 38.5 Gy total in 10 fractions (3.85 Gy per fraction), 2 a day with an interval of at least 6 hours between the two fractions, for 5 consecutive working days were administrated. In the control arm, 45 Gy/18 fractions, or 50 Gy/25 fractions, or 50,4 Gy/28 fractions, or isoeffective fraction schemes, once a day for five days a week were given. A 10 - 16 Gy boost was allowed in centers where it was part of the standard treatment.

Result: We report the preliminary analysis of a trial comparing partial with whole irradiation. This study has included 34 clinical institutions, referring to 23 Italian Centers and 11 International ones. So far, 2791 patients have been registered, 25 patients excluded, 2766 (83.8%) patients have been randomized of 3302 expected, 1381 of them are allocated to partial irradiation, and 1385 to whole irradiation. The results showed that the mean age between the two groups was similar; the histology and TNM classes were comparable. The majority of patients were T1N0 (81.5%), only 33.4% of patients had tumours < 1cm and 91.8% of patients were classified as N0. 10 (0.4%) patients experienced ipsilateral local recurrences. The local recurrence free survival was 99% at 5 years. 49% percent of women experienced acute toxicities, however no substantial high-grade skin toxicity was observed.

Conclusion: Given the preliminary nature of the analysis no information can yet be provided about the efficacy and safety of the treatments being compared. However the data suggest that the two groups are comparable in terms of baseline characteristics and the quality of data is good. The results obtained are in line with those expected.

Background: Nelle donne con tumore alla mammella a basso rischio di recidiva dopo chirurgia conservativa lLa radioterapia su tutta la mammella è considerata essere la terapia standard. Negli ultimi anni, una serie di nuove tecniche hanno permesso lo sviluppo della irradiazione parziale del mammella, con l'intenzione di migliorare il rapporto rischio beneficio della radioterapia al seno, in termini di minor tossicità, miglio cosmesi e compliance.

Obbiettivi: L'obiettivo primario è quello di valutare se l'irradiazione parziale ipofrazionata e accelerata della sola cavità chirurgica non è inferiore all'irradiazione postoperatoria con frazionamento convenzionale di tutta la mammella per quanto riguarda le recidive locale, misurata in termini di incidenza di recidive locali ipsilaterali come primo evento. Gli obbiettivi secondari sono il confronto delle due tecniche di irradiazione in termini di: a) sopravvivenza globale; b) libere da recidiva loco-regionale; c) la sopravvivenza libera da recidiva a distanza (tranne per le recidive locali e loco regionali o nella mammella controlaterale); d)risultati estetici; e) tossicità acuta.

Metodi: IRMA è uno studio randomizzato controllato finalizzato a confrontare la radiazione parziale ed accelerata con la tecnica tridimensionale (3D-CRT) verso la terapia standard nelle donne di età $\geqq$49 anni, ECOG 0-2, sottoposte a chirurgia mammaria conservativa per carcinoma della mammella invasivo, pT 1-2 (<3 cm di diametro) pN0-N1 M0 , unifocale, margini di resezione istologicamente negativi (2 mm) al primo intervento o dopo successivo ampliamento. Nel braccio sperimentale 38.5 Gy totali in 10 frazioni (3.85 Gy per frazione), 2 volte al giorno con un intervallo di almeno 6 ore tra le due frazioni, per 5 giorni lavorativi consecutivi. Nel braccio di controllo 45 Gy/18 frazioni, o 50 Gy/25 frazioni, o 50,4 Gy/28 frazioni , 1 volta al giorno per 5 giorni alla settimana, o a schemi di frazionamento iso-efficaci (è consentito boost di 10 – 16 Gy se utilizzato come trattamento convenzionale dal singolo centro partecipante).

Risultati: Riportiamo i risultati parziali dell'analisi dello studio, confronto tra irradiazione parziale con la totale. In questo studio sono inclusi 34 centri clinici, 23 centri italiani e 11 internazionali. Finora, sono stati registrati 2791 pazienti eleggibili, 25 pazienti sono stati esclusi, 2766 (83.8%) pazienti sono stati randomizzati dei 3302 previsti, 1381 di loro sono randomizzati nel braccio della radiazione parziale(PBI), e il 1385 nel braccio dell'irradiazione totale (WBI). I risultati hanno mostrato che l'età media tra i due gruppi era simile; le classi di istologia e TNM erano comparabili. La maggior parte dei pazienti era T1N0 (81.5%), solo il 33.4% dei pazienti ha avuto tumori minor di 1 centimetro e il 91.8% dei pazienti hanno

uno stato linfonoedale come N0. 10 (0.4%) pazienti hanno avuto la ricaduta locale ipsilaterale. La sopravvivenza libera da recidiva locale ipsilaterale è stata del 99% a 5 anni. 49% per cento delle donne ha sperimentato tossicità acuta, ma non è stata osservata nessuna tossicità cutanea di alto grado.

Conclusioni: Data la natura preliminare dell'analisi nessuna informazione e riportata riguardo all'efficacia e la sicurezza dei trattamenti a confronto. Tuttavia i dati suggeriscono che i due gruppi sono paragonabili in termini di caratteristiche al basale e la qualità di dati è buona. I risultati fino ad ora ottenuti sono in linea con quelli attesi.

1.2 The clinical trial

In this section is presented the randomized clinical trial in order to evaluate the trials evaluating the efficacy and safety of the intervention in health care and the statistical methods will be presented in section 1.18.

The aim of this chapter is to define what are the randomized controlled clinical trials and some concepts with which the statistical analysis work on data collected from a clinical trial.

Any experimental or observational investigation is motivated by a general problem that can be tackled by answering specific questions, associated with the general problem of the population.

In a clinical trial which aims to assess whether an "experimental" treatment is better than a "control" treatment, being this standard or placebo, the statistical methodology allows us to assess whether the observed difference between the two groups is random. If you observe a difference in the outcome of the study, it must first be able to distinguish whether it is simply the product of the natural progression of the disease and not the reflection of a real difference between the two groups. This question can be answered thanks to the statistical hypothesis testing.

In an experimental trial, the methodological aspects for the statistical analysis, the important elements of statistical inference, is the estimate and hypothesis testing.

The hypothesis testing, can not answer the question: "The difference, if it is not accidental, is it due to the treatment?" To this question in fact, you can only answer by evaluating if the design of the study has worked all measures to avoid distortions and confounding factors, being obviously the randomization of treatment principal method for this purpose.

In observational studies the possible presence of bias and confounding factors makes it very difficult to answer this question.

Finally, what matters most is that the study increases the knowledge of the phenomenon and in particular, for a trial of treatments, that there is a good degree of "evidence" effect which justifies the use of the experimental treatment of future patients. You want to know if that is the effect of the treatment and clinically relevant. The answer has to do with the planning of the study, in particular with the choice made by the investigator on the sample size and will be based on the estimate obtained and its accuracy. The key issue is the estimation method used in the analysis.

Connected to the issue of relevance there is a further question that arises researcher: "the results of this study are applicable to future patients?" which do not answer with statistics, but with consideration of the conditions in which you are studying (eligibility criteria diagnostic, therapeutic procedures, support and so on) and the evolution of knowledge emerged at the same time as others on the same pathology.

1.2.1 Randomized clinical trial

A clinical trial is an experiment on humans for the purpose of evaluating one or more potentially beneficial therapies where the investigator has control of some features of the trial.

- **Why Are Clinical Trials Needed?**
  - Most definitive method of determining whether a treatment is effective.
    - Other designs have more potential biases
    - One cannot determine on the basis of uncontrolled observation whether an intervention has made a difference to outcome.
  - Determine incidence of side effects and complications.
  - Therapy accepted with no trial!
- **Types of Clinical Trials:**
  - Randomized
  - Non-Randomized
  - Single Center
  - Multi Center
  - Phase I, II, III, IV Trials

A randomized controlled trial (RCT) is an experiment which has the aim of studying a new intervention or therapy. The subjects are randomly assigned to the arms, which generally are one treatment and one control, and the results are evaluated by comparing the effect of treatment in the randomized arms. There are two types of studies: experimental (or interventional) and observational (non-interventional).

The randomized controlled trials are placed in the second position after systematic reviews and meta-analysis of scientific evidence in the pyramid (Figure 1.1).

Figure 1.1: Scientific evidence

This type of study is characterized by being:

• trial: once recruited the population, on the basis of all the inclusion and exclusion criteria, occurs the effect of a treatment (for example, the administration of a drug) by comparing it with the effect of another different treatment (for example, another drug, no drug or a placebo).

• controlled: the subjects involved in the study are divided into two groups: the experimental group or the arm receiving the treatment, and the group or the control group receiving a different or no treatment. If a trial is done correctly (see experimental), the two groups are as homogeneous as possible, at least for all the variables at baseline, and therefore comparable.

• randomized: the allocation of the treatment of persons must take place by a random method (random). Randomization increases the likelihood that the vari-

ables are distributed uniformly in the arms of the study. In this way, the possible differences observed between the arms can be attributed to the treatment.

Randomization may be performed in different ways. The most rigorous method involves the application of certain protocols, so that the investigator can not predict the treatment assigned to each patient (numbered series of sealed envelopes, telephone allocation by a central office independent from the place of experimentation, use of special tables of random numbers). The randomization may also be carried out by groups of patients, in this case one speaks of clusters for randomization. When possible, neither the investigator nor the parties involved are aware of the treatment assignment (that is, both are blind, hence the term "double-blind") to reduce the likelihood that they are influenced. Patients may behave differently depending on the group to which they belong and caregivers might consider otherwise their conditions (eg for the better sense if you have a lot of expectations in the experimental treatment)[10].

The randomized controlled clinical trial is a prospective, so the trial is being conducted in parallel in the two groups and the results are analyzed at the end of the study[20].

1.2.2 Phases of clinical trials

Four phases of clinical trials and medicine development exist and are defined below. Each of these definitions is a functional one and the terms are not defined on a strict chronological basis[4].

An investigational medicine is often evaluated in tow or more phases simultaneously in different clinical trials. Also, some clinical trials may overlap two different phases.

A study in which the participants are assigned by chance to separate groups that compare different treatments; neither the researchers nor the participants can choose which group. Using chance to assign people to groups means that the groups will be similar and that the treatments they receive can be compared objectively. At the time of the trial, it is not known which treatment is best. It is the patient's choice to be in a randomized trial.

1.2.2.1 Phase I Studies

Phase I: Initial safety trials on a new medicine. An attempt is made to establish the dose range tolerated by volunteers for single and for multiple doses. Phase I trials are sometimes conducted in severely ill patients (e.g., in the field of cancer) or in less ill patients when pharmacokinetic issues are addressed. Pharmacokinetic trials are usually considered Phase I trials regardless of when they are conducted during a medicine's development.

1.2.2.2 Phase II Studies

Phase II clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.

1.2.2.3 Phase III Studies

Phase III studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.

1.2.2.4 Phase IV Studies

Phase IV: Studies or trials conducted after a medicine is marketed to provide additional details about the medicine's efficacy or safety profile. Different formulations, dosages, durations of treatment, medicine interactions, and other medicine comparisons may be evaluated.

1.2.3 The role of the RCT

The evidence to support the efficacy and safety of a health intervention are derived from randomized controlled trials (RCTs)[**?**]. Clearly shows the important role that the RCTs to evaluate the effectiveness of health interventions.

The 3 dimensions that affect the quality of RCTs are:

- Relevance: the degree of importance with respect to a particular issue.

- Internal validity - extent to which systematic error (bias) is minimized in clinical trials
  - Selection bias: biased allocation to comparison groups
  - Performance bias: unequal provision of care apart from treatment under evaluation
  - Detection bias: biased assessment of outcome
  - Attrition bias: biased occurrence and handling of deviations from protocol and loss to follow uprapresent
- External validity - extent to which results of trials provide a correct basis for generalization to other circumstances
  - Patients: age, sex, severity of disease and risk factors, comorbidity
  - Treatment regimens: dosage, timing and route of administration, type of treatment within a class of treatments, concomitant treatments
  - Settings: level of care (primary to tertiary) and experience and specialisation of care provider
  - Modalities of outcomes: type or definition of outcomes and duration of follow up

The clinical relevance of the study and the external validity depending on the characteristics of:

- P = population
- I = intervention
- C = comparison (compared with the experimental intervention)
- O = outcome

Internal validity concerns the question of the precision and repeatability of the results obtained with a trial. An experimentation, if carried out according to the rules, is able to minimize systematic errors (by selection bias, from loss to follow-up, etc.) And in general to ensure the fact that, if replicated in similar conditions, will provide the same results.

External validity is rather a question of the degree of generalizability of the results, that is, as these can then be effectively when treatment will be used in the general population (transferability). II Most of the time the patients studied in the trial are very selected patients and little representative of the target population. The same conditions in which they carry out experiments (for the treatment modalities, the checks carried out regularly, the patients adherence, etc.) Are certainly not the same where treatment is used in normal medical practice.

Some considerations that may increase the external validity of RCTs are for subgroup analyzes (pre-specified), and if the study population had the same disease of the population of interest is different but the level of risk, the treatment effect will the same direction but the entity will be different (because it is different basis risk).

1.3 Study protocol

Introduction

A protocol is a document that describes every part of a clinical study. The document is prepared with care to safeguard the health of the participants and to respond to specific research questions. The protocol describes the type of people who can participate in the study, the scheduling of tests, procedures, medications and dosages, as well as the duration of the study. During the trial, the investigators follow the protocol and patients are monitored regularly by the study personnel to verify the state of health, safety and efficacy of the treatment.

The protocol of a clinical trial must provide, in relation to the design of the study, its primary objective and the type of end-point chosen, the principles and statistical methods on which it will base the analysis of results, and in fact this one aspect crucial in the planning phase of a study. It requires the statistician doctor to identify the most efficient methods and able to turn data into information sufficient to answer the study questions. The answer, whether positive or negative (or not disprove the hypothesis under study) increase scientific understanding of

the phenomenon.

Every well-designed clinical trial requires a protocol. The study protocol can be viewed as a written agreement between the investigator, the participant, and the scientific community. The contest provide the background, specify the objectives, and describe the design and organization of the trial. Every detail explaining how the trial is carried out does not need to be included, provided that a comprehensive manual of procedures contains such information. The protocol serves as a document to assist communication among those working in the trial. It should also be made available to others on request.

The protocol should be developed before the beginning of participant enrollment and should remain essentially unchanged except perhaps for minor updates. Careful thought and justification should go into any change. Major revisions that alter the directions of the trial should be rare. If they occur, the rationale behind such changes needs to be clearly described.

1.3.1 An outline of a typical protocol is given:

1. Background of the study

2. Objectives

    (a) Primary endpoint and response variable

    (b) Secondary endpoint and response variables

    (c) Subgroup hypotheses

    (d) Adverse effects

3. Design of the study

    (a) Study population

        i. Inclusion criteria

        ii. Exclusion criteria

    (b) Sample size

(c) Enrollment of participants
    i. Information consent
    ii. Assessment of eligibility
    iii. Baseline examination
    iv. Intervention allocation (randomization method)
(d) Intervention
    i. Description and schedule
    ii. Measures of compliance
(e) Follow up visit description and schedule
(f) Ascertainment of response variables
    i. Training
    ii. Data collection
    iii. Quality control
(g) Data analysis
    i. Interim monitoring
    ii. Final analysis
(h) Termination policy

4. Organization

(a) Participation investigators
    i. Statistic unit or data coordinating center
    ii. Laboratories and other special units
    iii. Clinical center(s)
(b) Study administration
    i. Steering committees and subcommittees
    ii. Data monitoring committee
    iii. Funding organization

5. Appendix

(a) Definitions of eligibility criteria
(b) Definitions of response variables

1.4 The structure of an experimental study

Finally, there are problems related to the mode of presentation of the results of the studies in the literature. Insufficient quantity and quality of information in the articles may not allow the reader a critical evaluation of the validity of the study, also for the purposes of the applicability of the results to their medical practice. The main scientific journals in for authors rules, obliging themselves to a detailed description of the study design. In 2001, the CONSORT statement was published with the aim of providing clear rules for conduction and presenting a clinical trial. This statement is accompanied with an explanatory document that facilitates its use. The figure 1.2 shows the CONSORT flowchart. It provides in a transparent manner, the progression of the subjects included in the study through the various stages of testing, starting from enrollment until the end of their involvement.

The CONSORT statement, further revised in 2010, includes a checklist of 25 points which entitled the discussion, define the essential standard requirements for the submission of RCT. In Consort-statement.org site you can access the latest version of the full document (table 1.1).

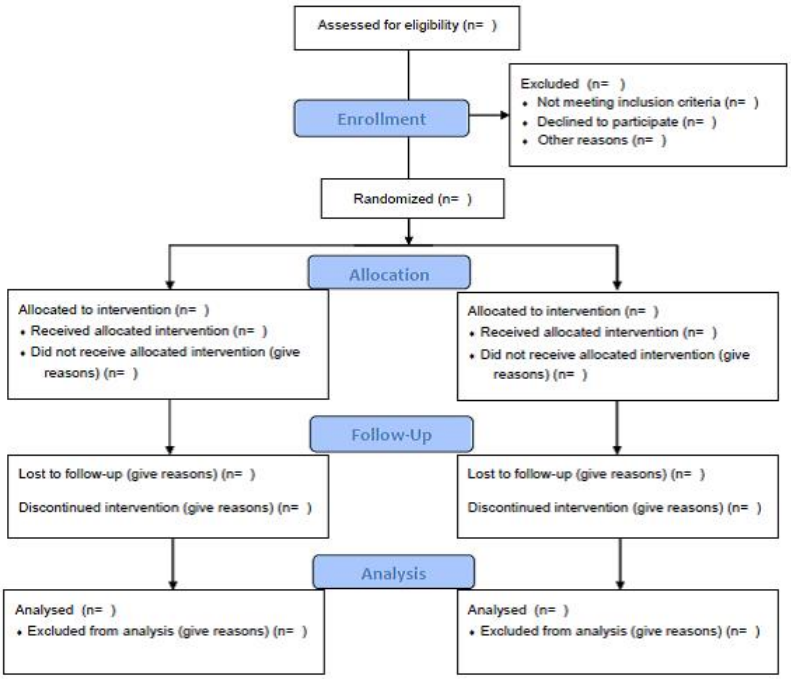

Figure 1.2: The COSORT flowchart

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org

Table 1.1: Checklist items of the CONSORT statement

1.5 The statistic analysis in an experimental study

It important that the data analysis is performed on all subjects initially recruited and that no patient is excluded from the study. At the end of the observation period for a trial it will be almost inevitable that some patients were not observed and evaluated for the whole period. This raises the question of how to treat the data for those patients who for various reasons have come out from the trial or who, for reasons of a different kind, have changed the treatment originally scheduled for their group membership. the information including those who did not follow the protocol, or who withdrew from the study, should be included in the final data. There is general consensus on the analysis performed according to the intention-to-treat (ITT analysis), so patients are evaluated according to the group to which they were assigned, regardless of the completion or not of the proposed treatment (that compares is the intention to treat). This principle makes it possible to evaluate the effectiveness of the treatment in real conditions, in which the patient may not adhere to treatment that has been assigned.

The data analysis according to the treatment actually received by patients who completed the trial (per protocol) evaluates the effectiveness of treatment instead of compliance under ideal conditions. In practice: a treatment could be very effective, but also produce a large number of dropouts due to side effects.

The intention to treat analysis is used to detect and quantify this aspect (which however do not emerge in the per protocol), scaling up the overall effectiveness and applicability of the treatment.

Three different approaches exist in the trial analysis:

- Per protocol analysis: is a comparison of treatment groups that includes only those patients who completed the treatment originally allocated. If done alone, this analysis leads to bias.

- "as treated", which means analyzing data on patients according to the treatment actually used;

- "Intention to Treat" (ITT), analysis is a comparison of the treatment groups that includes all patients as originally allocated after randomization. This is the recommended method in superiority trials to avoid any bias. For missing observations, “last value carried forward” is the recommended method.

In noninferiority trials, both intention to treat and per-protocol analysis are recommended; both approaches should support noninferiority.

1.6 Superiority, Equivalence, and Non-Inferiority Trials

When the aim of the randomized controlled trial (RCT) is to show that one treatment is superior to another, a statistical test is employed and the trial (test) is called a superiority trial (test). Often a non significant superiority test is wrongly interpreted as proof of no difference between the two treatments. In an equivalence trial, the statistical test aims at showing that two treatments are not too different in characteristics, where "not too different" is defined in a clinical manner. Finally, in a non-inferiority trial, the aim is to show that an experimental treatment is not (much) worse than a standard treatment.

The studies are divided according to their objective in:

- superiority trials
- equivalence trials
- non-inferiority trials

1.6.1 Superiority trial

The superiority trial have the objective to determine a clinically relevant difference between two intervention.

1.6.2 Equivalence trial

The equivalence trial have the objective to determine whether a (new) intervention in neither worse nor better than another (established) intervention. The researcher is disposed to accept an advantage but also a disadvantage, the experimental treatment than the standard, provided it can be demonstrated that they are maintained within certain margins clinically irrelevant.

1.6.3 Non-inferiority trial

The non-inferiority trial have the objective to determine if the experimental treatment provides a result not lower than that of the standard treatment; the researcher is disposed to accept a disadvantage of the experimental treatment than the standard, provided that it can demonstrate that it is kept within clinically irrelevant margins.

1.7 Methodology of statistical analysis

The present section describes the most relevant existing statistical approaches to analyzing the data set of an RCT. These methods will be assessed and the results of the IRMA trial will be presented in this chapter, section 1.18.

Why is statistic necessary?

There are two reason why some knowledge of statistics is an important part of the competence of every researcher, medical or other worker. First, statistical literacy is necessary if they are to read and evaluate reports and other literature critically and intelligently, enable the reader to decide the justification of the claims made by the particular author.

The importance of statistics in biomedical research is that we collect representative samples of subject, make measurements or observations on them, and then, by statistical analyses of data, draw inferences about the populations from which the samples were selected. Statistics also refers to the drawing of inferences about large groups on the basis of observations made on smaller ones.

The randomized clinical trial is the gold standard for some circumstances like evaluation of treatments, diagnostic procedures, or disease screening. The proper design and analysis of a clinical trial requires careful consideration of the study objectives (eg, whether to demonstrate treatment superiority or non-inferiority) and the nature of the primary end point. Different statistical methods apply when the end point variable is discrete (counts), continuous (measurements), or time to event (survival analysis).

This thesis provides an overview of the basic statistical approaches for analyzing clinical trials with binary, continuous or time-to-event outcomes.

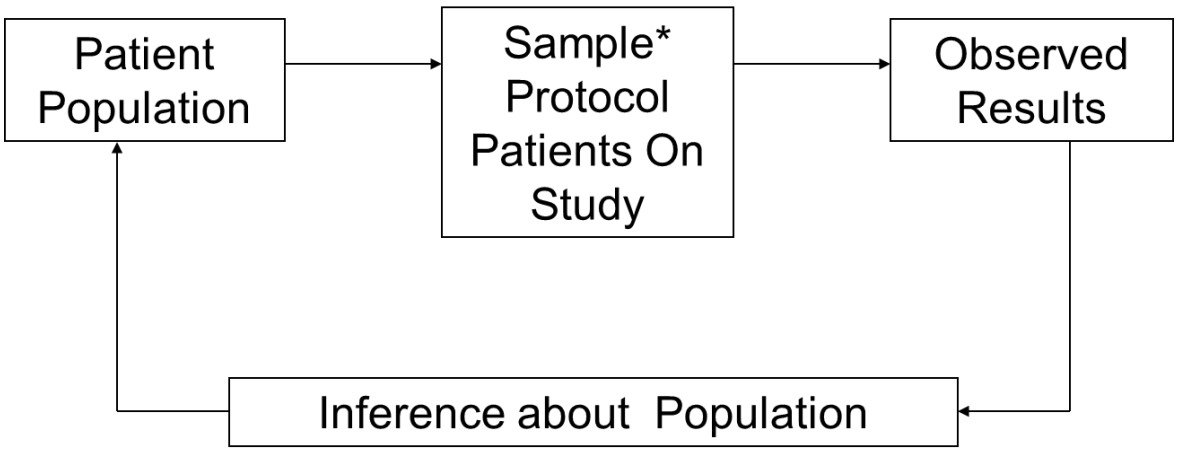

Figure 1.3: Flow of Statistical Inference

1.7.1 Definition and classification of statistical variables

Descriptive statistics are tabular, graphical, and numerical methods by which essential features of a sample can be described. Although these methods can be used to describe entire populations, they are more often applied to samples in order to capture population characteristics by inference. There are two main types of data samples: qualitative and quantitative data samples.

Classification of statistical variables

1. Quantitative variable: takes numerical values

   (a) Continuous and measurable: takes continuous values in an interval (temperature, height, weight, etc.)

   (b) Discrete or enumerable: takes integer values (number of patients, number of children, etc.)

2. Qualitative variable: takes no numerical values and takes coded numerical values

   (a) Ordinal: it is possible to ranking order (educational qualification, month, season, etc.)

(b) Nominal: there is no ranking order (men / female, alive / dead, etc.).

In the Table 2.1 we represent which statistical inference test to use for which type of data.

Goal	Dataset		
	Binomial or Discrete	Continuous measurement (from a normal distribution)	Continuous measurement, Rank, or Score (from non-normal distribution)
Example of data sample	List of patients recovering or not after a treatment	Readings of heart pressure from several patients	Ranking of several treatment efficiency by one expert
Describe one data sample	Proportions	Mean, SD	Median
Compare one data sample to a hypothetical distribution	χ^2 or binomial test	One-sample t test	Sign test or Wilcoxon test
Compare two paired samples	Sign test	Paired t test	Sign test or Wilcoxon test
Compare two unpaired samples	χ^2 square Fisher's exact test	Unpaired t test	Mann-Whitney test
Compare three or more unmatched samples	χ^2 test	One-way ANOVA	Kruskal-Wallis test
Compare three or more matched samples	Cochrane Q test	Repeated-measures ANOVA	Friedman test
Quantify association between two paired samples	Contingency coefficients	Pearson correlation	Spearman correlation

Tabella 1.2: Which statistical inference test to use for which type of data.

1.7.2 The measures of effect

The measures of the occurrence relationship or association between an effect and the outcomes are reported in the following paragraphs divided by type of end-point.

Effect: amount of change in the frequency of diseases caused by a specific factor.

Measuring the effect of a treatment it is performed by comparing the values assumed by a specific outcome variable (that is the dependent variable of the trial) between the groups formed with the randomization process.

1.7.3 The estimates of treatment effect

The fundamental purpose of a controlled experiment is to provide an estimate of an "experimental treatment" compared to a "standard treatment" (or placebo). In

the planning phase there are defined the end-point and some statistical means to express, in absolute or relative index, the effect of this difference. Such statistics, in general, will be based on a comparison between the effect of indexes in each treatment group.

1.7.4 Endpoint: dichotomous categorical variable

When the data to be analyzed consist of counts in a cross-classification of two groups (or conditions) and two outcomes, the data can be represented in a 2x2 table as follows:

	Treatment	Control	Total
Group 1	a	b	a+b
Group 2	c	d	c+d
Total	a+c	b+d	a+b+c+d

Risk in treatment group $P_t = \frac{a}{a+c}$

Risk in control group $P_c = \frac{b}{b+d}$

$$RR = \frac{P_t}{P_c} = \frac{a/a+c}{b/b+d}$$

$$RD = P_t - P_c = \frac{a}{a+c} - \frac{b}{b+d}$$

$$NNT = \frac{1}{RD}$$

$$ODDS_t = \frac{P_t}{1-P_t} = \frac{a}{c}$$

$$ODDS_c = \frac{P_c}{1-P_c} = \frac{b}{d}$$

$$OR = \frac{ODDS_t}{ODDS_c}$$

$$OR = \frac{\frac{a}{a+c}/\frac{c}{a+c}}{\frac{b}{b+d}/\frac{d}{b+d}} = \frac{a/c}{b/d} = \frac{ad}{bc}$$

Table 1.3: Measures of occurrence for evaluating the efficacy of a clinical trial

The calculation of the odds ratio is simply reduces to the product of the terms that are on the diagonals of the table 1.3.

The effect of the treatment measured in absolute terms the difference between the risks (Absolute Risk Reduction), and possibly translated into Number Needed

to Treat (number of patients who must be treated to achieve an event of interest), and preferable when you want to express the full extent that would the introduction of the experimental treatment in the patient population, since it directly expresses the number of preventable events.

The effect measured in relative terms is preferable when it is desired to express the effectiveness of the experimental treatment in terms of its effective ability to interfere with the disease compared to the control treatment.

ABSOLUTE MEASUREMENTS

The absolute measurement can be more easily contrasted to the evaluation of the costs relating to the introduction of the experimental treatment. The relative extent, taking into account the size, of the phenomenon in the control group, is more easily interpreted as a specific treatment effect also in several studies, with patients in different risk "baseline".

Several statistics can be calculated such as relative risk and risk difference, relevant in prospective studies, and odds ratio, relevant in retrospective case controls studies.

Risk difference

The risk difference(RD) can be seen as the absolute difference in the event rates of exposed and non-exposed people. RD as e attributable risk for the exposed, meaning of the portions of the incidence of given disease in the exposed that is due to the exposure.

$$RD = P_t - P_c = \frac{a}{a+c} - \frac{b}{b+d}$$

- DR > 0 - means essentially that the exposure is a potential risk factor
- DR = 0 - means that the exposure does not influence the disease
- DR < 0 - indicates that the exposure can be considered a potential protection factor

The recommended method for the calculation of the risk difference, which is a difference between proportions, requires the calculation of the confidence intervals of the two proportions separately[**?**].

The 95% confidence interval for the difference is given by

$$IC : \hat{RD} \pm z_{(1-\alpha/2)} es_{(\hat{RD})}$$

$$es_{(\hat{RD})} = \sqrt{\frac{(P_B(1-P_B)}{n_B} + \frac{P_A(1-P_A)}{n_A}} = \sqrt{\frac{ac}{(a+c)^3} + \frac{bd}{(b+d)^3}}$$

The risk difference - Measuring the effect of an exposure. Represents the quantity of risk attributable to the risk factor, the number of events among the exposed that could be avoided if it were removed the risk factor;

Number Needed to Treat

The number needed to treat (NNT) is the estimated number of patients who needed to treated with the new treatment rather than the standard treatment to prevent a bad outcome. A negative number for the number needed to treat has been called the number needed to harm

$$NNT = \frac{1}{RD}$$

If the two treatments are equally efficacy: DR = 0

RELATIVE MEASUREMENTS

Relative risk

In epidemiology, the concept of relative risk (RR) concerns ratio of the probability (risk) of the event occurring in the exposed group versus the probability of the same event in a non-exposed group.

In clinical trial the RR measures the probability of the occurrence of an event in the treated group compared to untreated, is a measure of the strength of the

association between factor and occurrence of the event. The relative risk is used to indicate the result of cohort studies or randomized trials.

The relative risk is the ratio of the proportions of cases having a positive outcome in the two groups.

The relative risk or risk ratio is given by

$$RR = \frac{P_t}{P_c} = \frac{a/a+c}{b/b+d}$$

- RR > 1 - means essentially that the exposure is a potential risk factor
- RR = 1 - means that the exposure does not influence the disease
- RR < 1 - indicates that the exposure can be considered a potential protection factor

We also need to calculate the 95% confidence interval (CI) of the RR, with the aim of controlling whether the value 1 is present in the interval. This is important because with the 95% CI containing the value 1, one cannot exclude, with 95% confidence, that the RR found is different from 1 (indifferent factor).

RR with the standard error of the log relative risk being and 95% confidence interval

Relative risk: as log(RR) - Normal

$$IC : log(\hat{RR}) \pm z_{(1-\alpha/2)} es(logRR) es_{(logRR)}$$

$$es_{(log\hat{RR})} = \sqrt{\frac{1}{a} + \frac{1}{a+c} + \frac{1}{b} + \frac{1}{b+d}}$$

an anti-logarithmic transformation conduct to RR scale

Relative Risk Reduction

$$RRR = \frac{p_B - p_A -}{p_B} = \frac{ARR}{p_b} = 1 - RR$$

Odds ratio

The odds Ratio (OR) simply presents the ratio between the odds of being exposed among cases and the same odds among controls. non-exposed. ODDS: number of events / number of non events in each group; The odds ratio is a good approximation of the RR in the case of rare diseases (a and c should be negligible). Odds Ratio is used in place of RR is not known when the real impact of the phenomenon (case-control studies, but sometimes controlled clinical studies).

The odds ratio is given by

$$OR = \frac{ODDS_t}{ODDS_c}$$

$$OR = \frac{\frac{a}{a+c} / \frac{c}{a+c}}{\frac{b}{b+d} / \frac{d}{b+d}} = \frac{a/c}{b/d} = \frac{ad}{bc}$$

- OR > 1 -means essentially that the exposure is a potential risk factor
- OR= 1 - means that the exposure does not influence the disease
- OR< 1 - indicates that the exposure can be considered a potential protection factor

with the standard error of the log odds ratio being and 95% confidence interval

Odds ratio:as log(OR) - Normal

$$IC : log(\hat{OR}) \pm z_{(1-\alpha/2)} es_{(log\hat{OR})}$$

$$es_{(log\hat{OR})} = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

an anti-logarithmic transformation conduct to OR scale

1.7.5 End-point: continuous variable

The parameter used to indicate the effect of each treatment is an indicator of central tendency, the mean or median. The most common measure of central tendency is the sample mean.

$$M = \frac{(x_1+x_2+....+x_n)}{n}$$

Also denoted $\bar{x}$,where $x_1, x_2, \ldots, xn$ is the collection of numbers from a sample of size n

The comparative effect of the treatment is expressed by the absolute difference between the means of the continuous variable in the two treatment groups, the following is the scheme of the estimator of the mean difference (MD) and its standard error, along with the confidence intervals.

The estimate in a randomized, two-arm, with end points corresponding to a continuous variable x and with the effect expressed as the difference between the averages.

Difference in means (mean difference)

$$MD = \mu_A - \mu_B$$

Estimate mean difference

$$\hat{MD} = \overline{x}_A - \overline{x}_B$$

It is the estimate of the effect of the experimental treatment A in comparison to the control B, where $\overline{x}$ is the arithmetic mean of the continuous variable x.

- MD > 0 - the treatment is less efficacy than the control
- MD = 0 - the two treatments are equally efficacy
- MD < 0 - the treatment is more efficacy than the control

Standard error

$$es_{(\hat{MD})} = \sqrt{\frac{\hat{\sigma^2}}{n_A} + \frac{\hat{\sigma^2}}{n_B}}$$

where $\hat{\sigma}^2$, variance in the population (in the presence of homoscedasticity), is estimated by

Variance

$$\hat{\sigma}^2 = \frac{(n_A-1)\hat{\sigma}_A^2+(n_B-1)\hat{\sigma}_B^2}{(n_A+n_B-2)}$$

Confidence interval

$$IC : \hat{MD} \pm z_{(1-\alpha/2)} es_{(\hat{MD})}$$

1.7.6 End-point: time to event analysis (survival analysis)

This chapter review some of the fundamental concepts and basic methods in survival analysis.

Fundamental points

Survival analysis methods are important in trial where participants are entered a period of time and have various lengths of follow-up. These methods permit the comparison of the entire survival experience during the follow-up and may be used for the analysis of time to any dichotomous response variable such as a nonfatal event or an adverse effect[**?**].

Survival analysis is used to analyze data in which the time until the event is of interest. The response is often referred to as a failure time, survival time, or event time.

In clinical trials the investigator is often interested in the time until participants in a study present a specific event or endpoint. This event usually is a clinical outcome such as death, disappearance of a tumour, etc.

The participants will be followed beginning at a certain starting-point, and the time will be recorded needed for the event of interest to occur. Usually, the end of the study is reached before all participants have presented this event, and the outcome of the remaining patients is unknown. Also the outcome is unknown of the participants who have withdrawn from the study. For these cases the time of follow-up is recorded (censored data).

Why Use a Kaplan-Meier Analysis?

- The goal is to estimate a population survival curve from a sample.
- If every patient is followed until death, the curve may be estimated simply by computing the fraction surviving at each time.
- However, in most studies patients tend to drop out, become lost to followup, move away, etc.
- A Kaplan - Meier analysis allows estimation of survival over time, even when patients drop out or are studied for different lengths of time.
- For each interval, survival probability is calculated as number of patients surviving divided by number of patients at risk. Patients who have died, dropped out, or not reached the time yet are not counted as "at risk." Patients who are lost are considered "censored" and are not counted in the denominator.
- Probability of surviving to any point is estimated from cumulative probability of surviving each of the preceding time intervals (calculated as the product of preceding probabilities) .
- Although the probability calculated at any given interval isn't very accurate because of the small number of events, the overall probability of surviving to each point is more accurate.

Kaplan - Meier survival curve

The Kaplan-Meier estimator of the survivorship function, also called the product limit estimator, is the estimator used by most software packages. This estimator incorporates information from all of the observation available, both uncensored and censored, by considering survival to any point in time as a series of steps defined by the observed survival and censored times.

This function estimates survival rates and hazard from data that may be incomplete.

The survival rate is expressed as the survivor function (S):

$$\hat{S}_t = \frac{number-of-individuals-surviving-longer-than-t}{total-number-of-individuals-studied}$$

where t is a time period known as the survival time, time to failure or time to event (such as death); e.g. 5 years in the context of 5 year survival rates.

Some texts present S as the estimated probability of surviving to time$t$ for those alive just before t multiplied by the proportion of subjects surviving to t. Thus it reflects the probability of no event before$t$. At $t = 0$ $S(t) = 1$ and decreases toward 0 as$t$ increases toward infinity.

The product limit (PL) method of Kaplan and Meier (1958) is used to estimate$S$:

$$\hat{S}_t = \prod_{t_i \leq t} \left[1 - \frac{d_i}{n_i}\right]$$

where $t_i$is duration of study at point$i$, d_i is number of deaths up to point$i$ andn_i is number of individuals at risk just prior to t_i.

S is based upon the probability that an individual survives at the end of a time interval, on the condition that the individual was present at the start of the time interval. S is the product$(P)$of these conditional probabilities.

If a subject is last followed up at time t_i and then leaves the study for any reason (e.g. lost to follow up)t_i is counted as their censorship time.

Assumptions:

- Censored individuals have the same prospect of survival as those who continue to be followed. This can not be tested for and can lead to a bias that artificially reduces$S$.

- Survival prospects are the same for early as for late recruits to the study (can be tested for).

- The event studied (e.g. death) happens at the specified time. Late recording of the event studied will cause artificial inflation of S.

The instantaneous hazard function $h(t)$ is defined as the event rate at time$t$ conditional on surviving up to or beyond time$t$. As h(t) is a rate, not a probability, it has units of $\frac{1}{t}$. The cumulative hazard function $\hat{H(t)}$ is the integral of the hazard rates from time 0 to t, which represents the accumulation of the hazard over time - mathematically this quantifies the number of times you would expect to see the failure event in a given time period, if the event was repeatable. So it is more accurate to think of hazards in terms of rates than probabilities.

The cumulative hazard is estimated by the method of Peterson (1977) as:

$$\hat{H}_t = -ln(\hat{S}_t)$$

1.7.7 Methodology for the agreement between two raters

The concordance can relate to not only the agreement is observed between two evaluation of the same patient, but also between two or more raters who evaluate the same outcome, or the same result in one of two different times evaluated by the same raters.

1.7.8 Kappa Cohen

Kappa (k) is commonly used in the medical literature to measure inter-observer variation. Cohen's kappa is a measure of the agreement (coefficient of agreement) between the qualitative or categorical responses of two raters (inter-observer variation), or the same raters at different times (intra-observer variation), considering the same subjects[21, 3].

The calculation is based on the difference between how much agreement is actually present ("observed" agreement) compared with how much agreement would be expected to be present by chance alone ("expected" agreement).

Let Io denote the observed value of the index, and let Ie denote the value expected on the basis of chance alone.

The obtained excess beyond chance in $Io - Ie$, whereas the maximum possible excess is $1 - Ie$. The ratio of these two differences is called kappa.

$$\hat{K} = \frac{Io-Ie}{1-Ie}$$

Agreement is quantified by the Kappa (K) or Weighted Kappa (Kw) statistic[**?**]

K is 1 when there is perfect agreement between the classification systems;

K is 0 when there is no agreement better than chance;

K is negative when agreement is worse than chance.

The K value can be interpreted as follows[**?**]:

Value of K	Strength of agreement
< 0.20	Poor
0.21 - 0.40	Fair
0.41 - 0.60	Moderate
0.61 - 0.80	Good
0.81 - 1.00	Very good

Table 1.4: Interpretation Kappa value

1.8 IRMA trial, an international randomized control trial evaluating the efficacy and safety of radiotherapy in women with breast cancer

1.8.1 The protocol of IRMA trial

Title of the IRMA trial

Breast cancer with low risk of local recurrence: partial and accelerated irradiation with three-dimensional conformal radiotherapy (3D-CRT) vs. standard radiotherapy after conserving surgery (phase III study).

Proposing operative units: radiotherapy operative units of Ancona, Bologna AOSP (hospital), Bologna AUSL (local health unit), Ferrara, Forli, Modena, Parma, Piacenza, Ravenna, Reggio Emilia, Rimini

Investigator: L. Armaroli BarbieriI E., F. Bertoni, L. Busutti, M. cardinals, F. Cartei, E. Emiliani, G. Frezza, M. Fumagalli, M. Giannini, F. Perini, M. Vanzo

Protocol authors : G. Frezza,F.Bertoni, R D'Amico

Data center office

Clinical Trials Office, Department of Oncology, Hematology and Pulmonary Diseases.

Polyclinic Hospital, University of Modena and Reggio Emilia

R. D'Amico, C. Del Giovane, R. Vicini

Tel. +39 059 4223865

roberto.damico@unimore.it

roberto.vicini@unimore.it

Coordinating Center:

Oncological Radiotherapy Operative Unit - Data Center Office, Clinical Trials Office, Integrated Department of Oncology, Hematology and Pulmonary Disease, Modena University Hospital.

Members of steering committee, the scientific committee and the monitoring committee

Steering Committee: G. Frezza, A.Martoni, M. Taffurelli, R. D'Amico, M. Pajusco, P. Chiovati, V. Eusebi.

Scientific Committee: L. Armaroli, E. Barbieri, F. Bertoni, L. Busutti, M. Cardinali, F. Cartei, E. Emiliani, G. Frezza, M. Fumagalli, M. Giannini, F. Perini, M.Vanzo, A. Liberati, D. Amadori, G. Natalini.

Independent Data Monitoring Committee: B. Gallo, V. Torri, R. Fossati, R. Orecchia, M. Valli.

Outline and synopsis

Surgery: Conservative surgery (including large breast resection and lumpectomy + biopsy of the sentinel lymph node and/or axillary dissection).

Evaluation of eligibility criteria (Chapter 4.3.5)

Recruitment and informed consent (Appendix II)

Stratification for:

1. size of T;
2. lymph nodes (N0 and N1);
3. chemotherapy (Yes, No).

Randomization (Chapter 4.3.12)

TREATMENT

Radiotherapy:

Trial arm 38.5 Gy total in 10 fractions (3.85 Gy per fraction), twice a day with an interval of at least 6 hours between the two fractions, for five consecutive working days.

Control arm 45 Gy/18 fractions, or 50 Gy/25 fractions, or 50,4 Gy/28 fractions, or isoeffective fraction schemes, once a day for 5 days a week. A 10 - 16 Gy boost is allowed in centers where it is part of the standard treatment.

Medical treatment

In patients who have not been previously treated with chemotherapy the radiotherapy must begin within 12 weeks from surgery. Whereas, for those who have been treated with chemotherapy the radiotherapy must start at least 2 weeks after the last chemotherapy cycle and no longer than 5 weeks after the end of chemotherapy. Hormonal therapy (tamoxifen, aromatase inhibitors) can be administered at the same time as the radiotherapy.

1.8.2 Synopsis of the IRMA trial

Title of the protocol

Breast cancer with low risk of local recurrence: partial and accelerated irradiation with three-dimensional conformal radiotherapy (3D-CRT) vs. standard radiotherapy after conserving surgery (phase III study).

Study Sponsor

This study was designed and developed within the Emilia Romagna Research and Innovation Program (PRI ER). The study does not have any commercial sponsor. It is considered an independent study according to the Ministerial Decree 17.12.2005. The PRI ER program guarantees a contribution to the study for the first three years of recruitment through the Regional Innovation Fund, which will cover the costs of coordination and data management sustained by the Coordinating Center.

Primary Objectives

The main aim of the study is to evaluate whether partial hypofractionated and accelerated irradiation of the sole surgical cavity, in patients suffering from breast cancer with low risk of local recurrence and undergoing conservative surgery, is not inferior to postoperative irradiation with conventional fractionation of the entire breast as regards local control, measured in terms of incidence of ipsilateral recurrences as first event.

Secondary Objectives

To compare the two methods of irradiation in terms of:

a) overall survival;

b) locoregional recurrence free survival (with exception of contralateral tumors and second tumors);

c) distant relapse-free survival (except for local or regional relapses or in the contralateral breast);

d) cosmetic results;

e) acute toxicity.

Two subsidiary projects concerning the economic and organizational impact of the treatment and its influence on the quality of life and psychosocial sphere of the patient (see subsidiary projects) will also be carried out.

Possible connection with other national and international studies

Similar studies are currently underway, however they evaluate different methods of partial irradiation.

Study Design

Multicenter, unblinded phase III, non-inferiority randomized controlled trial.

Number of centers and cases At the moment 34 radiotherapy centers are participating and recruitment of 3302 patients is planned.

Target Population of the Study

Women aged = > 49, ECOG 0-2, undergoing conservative breast surgery for invasive breast cancer, pT 1-2 (< 3 cm in diameter) pN0-N1 M0, unifocal, histologically negative resection margins ($\geq$ 2 mm) at first intervention or after subsequent widening.

Duration of the recruitment and of the subsequent follow-up

A recruitment of 3 years is planned and a follow-up period of 5 years for an overall duration of the study of 8 years.

Eligibility criteria (inclusion)

- Histologically confirmed invasive breast cancer;
- pT 1-2 (< 3 cm in diameter) pN0-N1 M0 according to TNM classification;
- Unifocal disease (confirmed radiologically and histologically);
- Eligible histotypes: all except for non-epithelial histotypes (lymphoma, sarcoma);
- Hormonal receptor status: indifferent
- Patients undergoing conservative breast surgery for neoplasms with a diameter < 3 cm and with biopsy of the sentinel lymph node or first instance axillary dissection;
- Breast resection margins histologically negative ($\geq$ 2 mm) at first intervention or after subsequent widening;
- Radiological examination of the surgical specimen to assess the excision of the hidden lesions and/or the microcalcifications if present in the mammography carried out before surgery
- Positioning of 3-6 metallic clips, or in any case of an appropriate number to delineate the area of surgical exeresis (tumor bed);
- At least two weeks must have elapsed from the end of the chemotherapy if this is administered before the radiotherapy;

- In patients who do not receive chemotherapy, radiotherapy should start < 12 weeks after surgery;
- No chemotherapy must be carried out during or at least two weeks after completion of the radiotherapy;
- Treatment with tamoxifen or aromatase inhibitors is allowed at the same time;
- Age $\geq$ 49 ·Gender: female;
- ·Menopause status: unspecified ·Performance status: 0-2 according to ECOG;
- Life expectation: at least five years ·INFORMED consent: yes;
- Non-hormonal contraception in patients of childbearing age;
- Patients technically eligible for radiotherapy (see paragraph 4.2.8.2).
-

Exclusion criteria

- In situ carcinoma (CLIS and DCIS);
- Non-epithelial breast neoplasms (sarcoma, lymphoma etc.);
- Micro/macrometastases in > 3 axillary lymph nodes; micro/macrometastases in the internal mammary and/or supraclavicular or subclavicular lymph nodes;
- Multicentric carcinomas (lesions in different quadrants of the breast or in the same quadrant but separated by at least 4 cm) or clinically or radiologically suspected lesions in the ipsilateral breast, unless their tumoral nature was excluded through biopsy or fine needle sample:
- Palpable radiologically suspected ipsilateral or contralateral axillary, supraclavicular or infraclavicular, internal mammary nodes (unless their tumoral nature was excluded through biopsy or fine needle sample);

- Treatments for previous contralateral or ipsilateral breast cancers;
- Paget's disease of the nipple:
- Cutaneous involvement, independently of the tumor diameter;
- Distant metastases;
- Previous radiotherapy on the thoracic region;
- Previous neoadjuvant chemotherapy;
- Collagen diseases (systemic erythematosus lupus, scleroderma, dermatomiositis);
- Other pathological conditions that limit life expectancy to < 5 years;
- Psychiatric diseases or disorders of other nature that prevent signing of informed consent for the treatment;
- Other neoplasms in the last 5 years with the exception of skin tumors apart from melanoma and squamous intraepithelial lesions (SIL) of the uterine cervix;
- Pregnancy and breast-feeding.

Treatment

The patients will be randomized to receive one of the following treatments:

Trial arm: 38.5 Gy total in 10 fractions (3.85 Gy per fraction), twice a day with an interval of at least 6 hours between the two fractions, for five consecutive working days.

Control arm: 45 Gy/18 fractions, or 50 Gy/25 fractions, or 50,4 Gy/28 fractions, or iso-effective fraction schemes, once a day for 5 days a week. A 10 – 16 Gy boost is allowed in centers where it is part of the standard treatment.

Endpoints

Primary: local ipsilateral recurrence as first event free survival

Secondary: overall survival, locoregional recurrence-free survival, distant recurrence-free survival, acute and late toxicity (RTOG) and cosmetic result.

Evaluation and Follow-Up Program

Clinical examinations are scheduled as follows: at the end of treatment, at 6 weeks, at 3 - 6 - 12 months from the end of the radiotherapy and then once a year until the end of the fifth year.

Data Analysis

Partial irradiation will be considered not inferior to the standard irradiation if the upper bound of the one-sided HR 95% confidence interval does not exceed the established value of 1.5.

The study was sized assuming that the percentage of local ipsilateral breast recurrences as first event at 5 years in the control arm is equal to 4% and setting error and equal respectively to 0.05 and 0.10.

The Kaplan-Meier method will be used to estimate the survival rates. The hazard ratio (HR), estimated by using the Cox model, will be reported as well as its one-sided 95% confidence interval.

The independent data monitoring committee (IDMC) will periodically receive reports about patient accrual rate, number of patients, events observed and toxicity.

If necessary, the IDMC will consider the possibility of an early suspension of the study.

Ethical Aspects and Informed Consent

Before entry onto the study, each patient will be informed about the investigational nature of the study, and a written informed consent, which has to have been previously approved by the institutional ethics committee, will be obtained.

The study will be carried out according to the ethical principles of the Helsinki Declaration and the GCP guidelines.

1.8.3 Introduction

1.8.4 Conservative breast surgery and radiotherapy

The association between surgery and radiotherapy constitutes the standard in conservative treatment of breast cancer. Many clinical studies, carried out in the last

30 years have made it possible to reach the conclusion that, in tumors with a diameter of less than 3 cm, the conservative treatment of the breast offers the same probability of local control of the disease as total mastectomy, provided that surgery is followed by radiotherapy.

Most of the guidelines propose administering a dose of around 45-50 Gy to the entire mammary gland; the most commonly used fractionation is 1.8-2.5 Gy per session for a total of 5 weekly sessions.

The safety of conservative surgery followed by conventional radiotherapy as defined above has been shown by several studies, with over 20 years of follow-up[7, 22], and meta analyses[15]. In these studies the estimated probability of local recurrence at 5 years was reported to be between 4 and 8%. All studies have shown that the mortality of the patients who underwent conserving surgery is not different from the mortality observed in patients who underwent a mastectomy[15].

Despite these studies and the existence of several guidelines suggesting the use of conservative surgery, it is still widely underused - especially in the less developed countries - mainly due to the unavailability of radiotherapy units. However, this tendency exists in the Western world as well. In the United States only 42% of patients with stage I-II breast cancer undergo conservative surgery. Furthermore, on average, over 20% of these patients do not subsequently undergo radiotherapy on the remaining breast[11].

This phenomenon is attributed to various factors, ascribable partly to the attitude of the physicians and partly to that of the patients. In fact, many physicians manifest a certain reluctance to consider conserving surgery appropriate in presence of positive axillary lymph nodes or in postmenopausal women. At the same time, patients tend to dislike a daily treatment lasting 5-6 weeks, which is not always associated with a satisfactory cosmetic result and could have some toxicity.

For these reasons a revision of the optimal standard characteristics of radiotherapy for breast cancer has recently been suggested. In particular, some centers have begun to study a technique of irradiation of the mammary gland designed, on one hand, to reduce toxicity through the use of sophisticated techniques such as three-dimensional conformal radiotherapy (3DCRT), intensity modulation radiotherapy (IMRT), brachytherapy and finally intraoperative radiotherapy (IORT) and, on the other hand, to accelerate the treatment administrating high-end doses by fraction, reducing then irradiated volumes (partial irradiation of the breast). A further advantage of these techniques is the reduction of possible cardiac and pulmonary toxicities[11].

1.8.5 Rationale of partial breast irradiation

The current philosophy at the basis of local treatment of breast cancer is based on treatment of the entire gland, with recourse to total mastectomy or associating radiotherapy on the remaining breast with conservative surgery.

It is widely held that an inadequate local treatment is associated with an increase in local recurrences, while the possibility that this increase can modify the risk of metastasis is still controversial. Indeed, radiotherapy after conservative surgery can reduce by 75% (or, in other words, by about 4 times) the risk of local recurrence[11]. On the other hand, at least 11 (eleven) randomized clinical studies of comparison between conservative surgery alone and conservative surgery plus radiotherapy have not demonstrated overall survival differences, although recent meta-analyses have reported that a better local control of the disease could be associated with a gain of about 3% in the survival at 10 years (EBCTCG 2000 Overview, unpublished data)[16, 14].

Irradiation of the breast in toto is proposed to prevent local recurrences, since it is considered that the entire volume of the breast is at risk. In support of the effectiveness of treatment of the entire breast the works of Holland are cited, in which a broad histological evaluation of the surgical samples of mastectomy in clinically unifocal tumors up to 5 cm in diameter had shown the presence of multifocality in 63% of the patients and in particular the presence of tumor foci at over 2 cm distance from the main tumor in 43% of the breasts examined[12]. In this context, however, it was recently shown how, thanks to better preoperative definition of the multifocal lesions due to superior mammography qualitative standards, at least some of the patients in Holland's study would not be candidates today for conservative surgery[1]. Furthermore, more recent histopathological studies suggest that in patients, who are candidates for conservative surgery according to the current guidelines, the microscopic spread of the disease more than 1 cm from the surgical resection margins is improbable[6, 5, 13, **?**].

Another datum in support of partial irradiation of the breast derives from the fact that most of the local recurrences are in the breast quadrant where the original neoplasia was located, independently of the fact of whether the patient undergoes radiotherapy or not. According to a recent review of about 10,000 cases, this percentage would be 71%[9], according to the data of the NSABP B-06 study in which 75% of local recurrences occurred not far from the original tumorectomy[8]. On the contrary, if patients who underwent conservative surgery are considered as a

whole, only 3.3% of these develop a recurrence in a quadrant other than that initially affected by the tumor. Indeed, the natural history of the disease suggests that the homolateral recurrence of the neoplasia outside the quadrant affected should be considered as second tumor rather than a local recurrence. In confirmation of this, the disease-free period of the local recurrence developed at distance from the initially affected quadrant is generally superior to 5 years, a datum totally comparable with the average period of appearance of a second tumor of the contralateral breast. Furthermore, since the rate of recurrences appearing in a quadrant other than the original one does not differ between patients undergoing radiotherapy or not, the real preventive effect of radiotherapy on hidden tumoral microlesions that might be present outside the index quadrant appears doubtful to say the least[9].

In summing up, extensive trial evidence supports the effectiveness of a radiotherapeutic technique aimed at obtaining the sterilization of the sole tumor bed, at least in a selected group of patients. In this way it would be possible to decrease the volume of irradiation and, consequently, the number of fractions administered. The increase in the dose by fraction and the drastic decrease of the duration of the treatment could thus be obtained with a foreseeable decreased toxicity as well as all the overall benefits of the actual treatment.

1.8.6 Partial Breast Irradiation Methods

The partial irradiation technique can be subdivided into two major categories:

A) Intra/perioperative techniques: provide for the administration of the dose using an electron beam directly corresponding to the tumor bed through the use of dedicated accelerators or through perioperative curietherapy at high or low dose rate.

B) Postoperative techniques: administered on a reduced volume (classic curietherapy of the tumor bed or through MammoSite®, external three-dimensional conformal radiotherapy or with intensity modulation).

As regards external radiotherapy on the tumor bed alone, the first trials to appear in the literature were of the Manchester group and were published from 1982 to 1987[23, 18]. A total of 713 patients were randomized in 2 groups made up of postoperative irradiation of the sole quadrant affected by the neoplasia and conventional irradiation of the total volume of the breast. No patient underwent chemotherapy or hormone therapy; with an average follow-up of 65 months the

local recurrence rate was respectively 15 and 11% for the infiltrating ductal carcinomas and respectively 34% and 8% for infiltrating lobular carcinomas.

Recently the William Beaumont Hospital radiotherapist team[19] developed a conformal radiotherapy technique in which doses of 34 to 38.5 Gy were administered in 10 fractions and 5 days of treatment; this fractionation of the dose was calculated through the use of the "quadratic linear model" that establishes the equivalence of doses for different fractionations with foreseeable isoeffect from a biological point of view[2].

The target volume is made up of the tumor bed shown through appropriate clips placed by the surgeon – called “gross tumor volume” (GTV) -, then a safety margin of 15 mm, called “clinical tumor volume” (CTV) - that takes into account the presence of possible microscopic disease foci. The “planning tumor volume” (PTV) is made up of a further 10 mm margin to be added to the CTV in order to take into account respiratory excursions and the uncertainty of the placement. With this technique up to 31 patients have been treated until now and, with an average follow-up of 10 months, the toxicity, the cosmetic result and the local control observed were considered satisfactory. This trial gave rise to a phase II study of the RTOG, concluded a few months after recruitment of approximately 70 patients. Currently underway, also promoted by the RTOG, is a phase III randomized study (RTOG 0413 and NSABP B39) that compares conventional postoperative irradiation with hypofractionated and accelerated partial irradiation carried out by various methods (3D CRT, interstitial brachytherapy, Mammosite®).

1.8.7 Objectives of the study

Primary Objective

The main aim of the study is to evaluate whether partial hypofractionated and accelerated irradiation of the sole surgical cavity, in patients suffering from breast cancer with low risk of local recurrence and undergoing conservative surgery, is not inferior to postoperative irradiation with conventional fractionation of the entire breast as regards local control, measured in terms of incidence of ipsilateral recurrences as first event.

Secondary Objectives

To compare the two methods of irradiation in terms of:

a) overall survival;

b) locoregional recurrence free survival (with exception of contralateral tumors and second tumors);

c) distant relapse-free survival (except for local or regional relapses or in the contralateral breast);

d) cosmetic results;

e) acute toxicity.

Limiting the radiotherapy to the cavity of the tumorectomy and to its near vicinity, could allow for:

- A drastic reduction in the duration of the radiotherapy.

- Local control of the disease comparable with that of conventional treatment.

- Less toxicity at the level of the organs at risk (OAR) and the cutaneous and subcutaneous tissues.

- The patients will better accept and remain in the treatment

- Reduction of local non-optimal treatments (mastectomies in patients who are candidates for conserving surgery, conserving surgery not followed by radiotherapy).

The study also provides for the initiation of two subsidiary projects concerning the economic and organizational impact on the treatment and its influence on the quality of life and psychosocial sphere of the patient (see subsidiary projects).

1.8.8 Eligibility criteria

- Histologically confirmed invasive breast cancer
- pT 1-2 (< 3 cm in diameter) pN0-N1 M0 according to TNM classification.
- Unifocal disease (confirmed radiologically and histologically)
- Eligible histotypes: all except for non-epithelial histotypes (lymphoma, sarcoma)
- Hormonal receptor status: indifferent
- Patients undergoing conservative breast surgery for neoplasms with a diameter of < 3 cm and with biopsy of the sentinel lymph node or first instance axillary dissection.

- Breast resection margins histologically negative ($\geq$ 2 mm) at first intervention or after subsequent widening
- Radiological examination of the surgical specimen to assess the excision of the hidden lesions and/or the microcalcifications if present in the mammography carried out before surgery
- Positioning of 3-6 metallic clips (or an appropriate number of them) to delineate the area of surgical exeresis (tumor bed)
- At least two weeks must have elapsed from the end of the chemotherapy if this is administered before the radiotherapy. In patients who do not receive chemotherapy, radiotherapy should start < 12 weeks after surgery.
- No chemotherapy must be carried out during or at least two weeks after completion of the radiotherapy
- Treatment with tamoxifen or aromatase inhibitors is allowed at the same time

- Age $\geq$ 49 ·Gender: female ·Menopause status: unspecified
- Performance status: 0-2 according to ECOG
- Life expectation: at least 5 years ·Informed consent: yes
- Non-hormonal contraception in patients of childbearing age
- Patients technically eligible for radiotherapy (see paragraph 4.2.8.2)

1.8.9 Exclusion criteria

- In situ carcinoma (CLIS and DCIS)
- Non-epithelial breast neoplasias (sarcoma, lymphoma etc.)
- Micro/macrometastases in > 3 axillary lymph nodes; micro/macrometastases in the internal breast and/or supraclavicular or subclavicular lymph nodes

- Multicentric carcinomas (lesions in different quadrants of the breast or in the same quadrant but separated by at least 4 cm) or clinically or radiologically suspected lesions in the ipsilateral breast), unless the tumral nature was excluded through biopsy or fine needle sample.
- Palpable lymph nodes or radiologically suspected in situ: contralateral axillary, superclavicular or infraclavicular, internal breast (unless the tumoral nature was not excluded through biopsy or fine needle sample)
- Treatments for previous contralateral or ipsilateral breast cancers
- Paget's disease of the nipple
- Cutaneous involvement of disease, independently of the tumor diameter
- Distant metastases
- Previous radiotherapy on the thoracic region
- Previous neoadjuvant chemotherapy
- Collagen diseases (systemic erythematosus lupus, scleroderma, dermatomiositis)
- Other pathological conditions that limit life expectancy to < 5 years
- Psychiatric diseases or of another nature that prevent signing of informed consent for the treatment
- Other neoplasias in the last 5 years with the exception of skin tumors apart from melanoma and squamous intraepithelial lesions (SIL) of the uterine cervix
- Pregnancy and breast-feeding

1.8.10 Pre - treatment evaluations

- Personal and family case histories, including familiarity for breast cancer and types of diagnoses of the neoplasia (clinical, mammography, both...)
- Physical examination with the description of the location of the neoplasia and the diameter of the tumor in cm.
- Bilateral mammography and/or breast ultrasound examination with measurement of the lesion
- Thorax x-ray, blood chemistry, serum markers (Ca 15.3 and CEA)
- Liver ultrasound/bone scan in case of suspicion of hepatic/bone lesions.

1.8.11 Radiotherapy

1.8.11.1 Phases of the 3D-CRT irradiation technique implementation program

- Definition of an appropriate Clinical Target Volume (CTV). To this end it is fundamental that in all the patients who are candidates for the study an appropriate number of clips have been placed by the surgeon (generally from 3 to 6) oriented according to the three spatial axes (x,y,z) to accurately display the tumor bed to the CT on which the radiotherapist will encircle the target volume.
- Definition of the maximum doses for the organs at risk (OAR) including the entire homolateral breast, the contralateral breast, the lungs, the heart and the skin.
- Definition of a treatment technique that is a just compromise between complexity and daily reproducibility in such a way as to obtain as homogenous as possible a distribution of the dose, minimizing exposure of the critical organs.
- Definition of an appropriate Planning Target Volume (PTV) that takes into account the uncertainty of position, setup errors and respiratory movements.

- Implementation of a quality control protocol.
- Evaluation of the tolerance to the treatment with accurate monitoring of the toxicity and with appropriate follow-up program.

1.8.11.2 Care plan, simulation and treatment technique

Trial arm

All the patients will undergo computerized tomography (CT) to prepare the treatment plan. The patient will be made to lie on an appropriate immobilization aid; subsequently "slices" of no more than 5 mm thick will be obtained with reconstruction at least every 5 mm from the mandible to the diaphragm: This deliberately large segment is such so as to allow the physicians to carry out the necessary treatment plans with non-coplanar fields.

The CT images will be transferred to the treatment plan system for the subsequent orientation of the targets and the OAR.

The appropriate CTV for partial irradiation of the breast is still under discussion: From the data available in literature it would seem that a margin of between 10 and 20 mm would be sufficient to include possible remains of the disease in the selected patients.

RTOG trial 95-17 presented to the 2002 ASTRO recommends a margin of 20 mm at the level of the lateral surgical margins and 10 mm at the level of the cranial and caudal surgical margins as well as a margin of 5 mm from the skin surface in order to minimize possible post-actinic teleangiectasias.

In the study the GTV (represented by the area of the surgical exeresis that can be seen through appropriate surgical clips) will be expanded isotropically by 15 mm in order to obtain the CTV. This expansion will be limited however towards the skin and the thoracic wall so that the distance between the CTV and this structure is not less than 5 mm. (The thoracic wall must not be included in the CTV; theoretically the muscles are not part of the CTV, although, in situations in which the clips are located near the actual muscles and the front limit of the muscles is not well identifiable, it may be inevitable to include them at least in their most forward part.).

Studies carried out on the respiratory movements of the thoracic wall (15) advise adopting a safety margin of 5 mm to be added to the CTV to compensate the respiratory excursions, while an additional margin of 5 mm would be sufficient to

compensate any setup errors. A further margin of 10 mm will thus be added to the CTV in order to obtain the PTV. This PTV (plus a few mm of margin in each direction for the penumbra) will be used to define the beam aperture. Since a good part of the PTV can extend outside the patient, a PTV EVAL will be obtained by editing and deleting from the PTV the part placed outside the patient and up to 5 mm of the skin, as well as the thoracic wall and the pectoral muscles (see also above). This PTV will be used for the evaluation of the dose distribution.

N.B.: The patients can be included in the study only if the CTV is < 30% of the breast volume. Therefore the CT will be carried out before requesting from the patient consent for participation in the study and before randomization. The breast volume will be defined identifying as such on the planning CT the volume included in two normal tangential fields, excluding the lung, and therefore usually the volume of healthy tissues included tangentially in front of the thoracic wall and which passes through the sternal medial and axillary medial lines. This volume will have as upper limit the transversal plane that passes through the lower edge of the sternal end of the clavicle and as lower limit the transversal plane that passes 1 cm under the crease of the breast.

The following organs at risk must also be contoured:

- Homolateral breast (for reference volume: see above)
- Contralateral breast (only the glandular parenchyma)
- Homolateral lung
- Contralateral lung
- Heart (only the heart chambers)
- Thyroid

As regards the treatment technique it is possible to carry out treatment plans with 4 or 5 possibly non-coplanar fields through use of > 4 MV photons with isocentric technique[2].

The fractionation proposed is 38.5 Gy per fraction administered twice daily with an interval of at least 6 hours between the two fractions in 5 consecutive days for a total of one week of treatment. The dose will be prescribed according to the ICRU

criteria. Algorithms must be used for the calculation of the dose distribution, taking into account lack of homogeneity in the tissues.

Control arm

In order to set the treatment plan all the patients will undergo computerized tomography (CT).

The patient will be made to lie on an appropriate immobilization aid; subsequently "slices" at intervals of no more than 5 mm will be obtained from the base of the neck to the diaphragm: The CTV is made up of the entire breast with the exclusion of the skin, which is not part of the breast. The OARs are represented by the homolateral lung and, in the case of the left breast, by the heart. The treatment technique recommended consists of two tangential fields of high-energy X-photons (> 4 MV) with possible homogenization of the dose distribution through wedge filters. The total dose for the breast is between 45 Gy/18 fractions, 50 Gy/25 fractions, 50.4 Gy/28 fractions or isoeffective fraction schemes. The possible boost can be with direct field of appropriate energy electrons and with reduced dimensions tangential fields. The overdosage dose will be between 10 and 16 Gy in the 5-8 fractions. In all cases the dose will be prescribed according to the ICRU criteria. Algorithms must be used for the calculation of the dose distribution, taking into account lack of homogeneity in the tissues.

1.8.11.3 Dose constraints

Trial arm

The dose administered to the OAR will be:

- homolateral breast: <60% of the breast should receive >50% of the prescribed dose and < 35% of the breast should receive 100% of the prescribed dose;
- $\leq$ 3% of the prescribed dose for the entire volume of the contralateral breast;
- >30% of the prescribed dose administered to < 15% of the homolateral lung;
- > 5% of the prescribed dose to < 5% of the heart volume for lesions of the right breast;
- > 5% of the prescribed dose to < 40% of the heart volume in lesions of the left breast;

- < 5% of the prescribed dose to the entire thyroid volume.

Control arm

The dose administered to the OAR will be:

- >30% of the prescribed dose administered to < 30% of the homolateral lung;
- > 50% of the prescribed dose to < 15% of the heart volume in lesions of the left breast.

1.8.12 Quality controls

1.8.12.1 Ensuring quality of dose distribution

Any treatment will be considered acceptable if:

Trial arm

- At least 90% of the PTV EVAL receives > 90% of the prescribed dose
- The DVH to the critical organs are within 5% of the specified values
- The maximum dose does not exceed 120% of the prescribed dose.

Control arm

- The DVH to the critical organs are within 5% of the specified values;
- At least 90% of the CTV receives > 95% of the prescribed dose;
- < 10% of the PTV receives > 110% of the prescribed dose;

1.8.12.2 Ensuring quality of positioning

Particular care will be devoted to positioning of the patient.

Trial arm

During the first session and at least once more during the course of treatment two orthogonal portal images will be acquired, at 0° and 90° (or 270°) that will be directly compared with two simulation images obtained in the same geometrical conditions or with total orthogonal DRR images obtained through the use of the CT sections on which the sample volume was oriented (DRR). The adequacy of the margins chosen for the PTV will be verified comparing the simulation or DRR images with the portal images.

Control arm

During the first session and at least once more during the course of treatment the portal images will be acquired at each of the tangential fields that will be directly compared with two simulation images obtained in the same geometrical conditions or with two DRR images obtain through the use of the CT sections on which the sample volume was oriented (DRR). The adequacy of the margins chosen for the PTV will be verified comparing the simulation or DRR images with the portal images.

A quality assurance program is also planned to document the adequacy of the treatments carried out and the data collected (see annex on the Quality Assurance Program of the Study)

1.8.13 Evaluation of the patients

1.8.13.1 Evaluation schedule

Evaluation	Basal	During RT	End of RT	At 6 wks	At 3 months	At 6 months	At 1 year
Visit	x		x	x	x	x	X (b)
Weight	x				x	x	x
Disease status	x		x	x	x	x	x
Mammography	x						X (a)
Breast CT	x						
Toxicity (c)	x	x	x	x	x	x	X (b)
Photographs	x				x	x	X (d)
Cosmetic evaluation (Patient)	x				x	x	X (d)
Cosmetic evaluation (Radiotherapist)	x					x	X (d)

Table 1.5: Evaluation schedule

a) Then annually.

b) From the end of the radiotherapy examination every 6 months for the first 3 years and then annually for at least 5 years.

c) See RTOG toxicity tables attached.

d) Then annually

1.8.13.2 Definitions of the type of cosmetic result

The cosmetic result will be evaluated by the patient and by the radiotherapist at 6 and 12 months after completion of the radiotherapy and subsequently annually according to the following parameters:

A) Excellent: minimum difference in relation to the untreated breast in volume, form, outline and consistency of the gland. Moderate thickening of the skin or scar tissue of the breast or the skin, but insufficient to modify its aspect.

B) Good: slight asymmetry in the volume or form of the treated breast in relation to the normal one. The thickening or the scar tissue in the breast produces only a

slight change in its form.

C) Fair: There is a clear difference in the volume and form of the breast treated. This change involves 1/4 or less of the breast.

D) Poor: marked modification of the aspect of the breast treated in over 1/4 of the breast tissue.

1.8.13.3 Evaluation of side effects, sequels and complications

In order to accurately evaluate the side effects, sequels and complications if any of the radiotherapy the RTOG toxicity tables will be used (annex 1).

1.8.13.4 Treatment efficacy clinical criteria

- The definition of failure of the treatment is constituted by the histological or cytological diagnosis of recurrence of breast cancer either invasive or non-invasive (excluding in situ lobular carcinoma) in the homolateral breast.

- A clinical examination or a suspect mammography will not be considered proof of failure of treatment in the absence of confirming biopsy or fine needle sample.

- Recurrences of the disease in the homolateral breast will be considered true and actual local recurrences (within the field of treatment) if they occur within the prescribed isodose volume, while they will be considered peripheral if they occur between the volume and a volume of 2 cm outside the prescribed isodose volume. However, they will be considered not contiguous or outside the field if they are more than 2 cm outside the prescribed isodose volume.

- Axillary homolateral, superclavicular, internal breast or supraclavicular recurrences or distant metastases will be considered a distant failure of the treatment if not accompanied by a synchronous homolateral breast recurrence.

1.8.14 Planned recruitment and statistical considerations

The sample size was estimated in relation to the rate of ipsilateral local breast recurrences as first event at 5 years, which represents the primary outcome of the study. Given the characteristics of the patients considered eligible and on the basis of the information derived from the literature, it is expected that the rate in the standard treatment group will be between 4% and 7%. Evaluations on the incidences of recurrences in the EORT trial[17] give values at 5 years of approximately 5%. Since this is a study of non-inferiority it was established that partial irradiation can be considered not inferior to standard radiation if the hazard ratio, calculated as ratio between recurrence hazard in the group that receives the partial treatment divided by the recurrence hazard in the group that received standard irradiation, is no greater than 1.5. This value corresponds, if the recurrence rate in the standard irradiation group is 4%, to a maximum recurrence rate value in the partial irradiation group of 6%. On the basis of this hypothesis a sample size of 1651 patients by arm for a total of 208 events (=0.05, one tail, and =0.10) was planned. With the same HR, if the recurrence rate at 5 years in the standard arm is higher, the size of the sample decreases perceptibly, as reported in Table 1.6. We considered the first scenario as a more probable one. The estimate of the sample was carried out using nQuery Advisor 6.0 statistical software.

Standard Irradiation	Partial Irradiation	α= 0.05 (one tail), β=0.1		
Recurrence rate 5 years (%)	Recurrence rate 5 years (%)	HR	N pts per arm	N total events
0.04	<0.06	<1.5	1651	208
0.05	<0.08	<1.5	1296	208
0.06	<0.09	<1.5	1172	208
0.07	<0.100	<1.5	986	208

Table 1.6: Estimate sample size

Primary analysis: The primary aim of the study is to assess the non-inferiority of partial radiotherapy in relation to standard radiotherapy in relation to the first ipsilateral recurrence. The time to the event is considered as the time elapsing between the date of the randomization and the date of the recurrence, understood as date of onset of the suspected recurrence then confirmed with cyto-histological diagnosis (see paragraph 8.5). The recurrence-free survival will be calculated using the Kaplan-Meier method. The hazard ratio (HR) will be estimated using the Cox

model and its one-sided confidence interval at 95% will also be reported.

Partial irradiation will be considered not inferior to the standard irradiation if the upper bound of the one-sided HR confidence interval at 95% does not exceed the established value of 1.5.

Secondary analyses: The evaluations of the esthetic results and the complications affecting the adjacent tissues and structures (lungs, heart, thoracic wall, contralateral breast) will be carried out comparing the results observed in the two arms at the various time points, taking into consideration the basal values.

The two groups will also be compared in relation to the following outcomes:

a) Distant recurrence-free survival (except for local or regional recurrences or in the contralateral breast);

b) Recurrence-free survival (with exception for contralateral tumors and second tumors);

c) Overall survival.

The interim analyses will be carried out annually from the occurrence of the 50th event of the principal outcome – however, the overall survival will also be evaluated. About 5 interim analyses are planned. The comparison between groups, in each analysis, will be examined using an endpoint test, with a statistical significance level equal to 0.001, according to the method proposed by Haybittle-Peto.

An independent data monitoring committee has been set up to assess the quality of data. The committee, made up of independent members, will receive periodic reports from the data center and will send its comments and recommendations to the study steering and scientific committees.

The independent data monitoring committee, if necessary, will consider the possibility for an early suspension of the study.

1.8.15 Randomization procedures

The randomization will be carried out at the data center office of the Modena University Hospital, Oncology Department, and will take place by WEB (www.irmatrial.it).

Patients eligible for inclusion will be randomized according to 3 stratification factors: lymph nodes (N0 and N1), size of T (T1 and T2) and chemotherapy (yes, no).

1.8.16 Ethics committee

Prior to recruitment the patients must sign an informed consent suitably drafted and submitted for the approval of the Ethics Committee (appendix I) The clinical study will be carried out according to the ethical principles of the Helsinki declaration and the GCP guidelines.

It is necessary before the formal initiation of the study that the study receives the approval from the Ethics Committee of the proposing center. The individual investigators of the different participating institutions are directly responsible for the submission of the protocol to their Ethics Committees.

An independent data monitoring committee, a scientific committee and a steering committee have been set up. The independent data monitoring committee, made up of independent members, will receive periodic reports from the data center office and will send its comments and recommendations to the steering committee and to the scientific committee of the study. The independent data monitoring committee will meet once a year and on the basis of the interim analyses will evaluate the possibility of an early suspension of the study.

The steering committee has the scientific ethical and coordination responsibility of the study, has to keep in touch with the monitoring committee and with other international and national centers carrying out like studies.

The committee is also responsible for the decisions relating to:

a) possible modifications of the protocol;

b) possible early suspension of the study;

c) maintaining relations with the ethics committees and with the coordination and data collection center;

d) the publication and dissemination of the results.

The scientific committee is responsible for the correct management of the study, both of the scientific aspects and conducting the research.

1.8.17 Rules for publication

The registration and data collection sheets will be collected at the Data Center Office in Modena, which will also be in charge of the data analysis.

An appropriate committee will have the task of drawing up and distributing the preliminary and final results of the study and will be responsible for drawing up of scientific works for any publications after prior internal discussion among the participants in the study.

The publication of the results is planned even if the results are negative. The authors of the scientific works will be acknowledged according to their contribution; however, all the names of the investigators and their institutions will be listed in a special appendix to the articles published.

1.8.18 Subsidiary projects

The study provides for the initiation of two subsidiary projects concerning the economic and organizational impact of the treatment and its influence on the quality of life and psychosocial sphere of the patient. The centers that have an adequate organizational and functional structure can join both subsidiary projects.

The first subsidiary project concerns the evaluation of the economic and organizational impact of partial irradiation of the breast with accelerated and hypofractionated fractionation. The assessment will concern the use of personnel and equipment, times of development and carrying out of the treatment and the possible spin-offs of the work loads on the radiotherapy institutes.

The second subsidiary project will evaluate the impact of the treatment on the quality of life and on the psychosocial sphere of the patients. It will be carried out through the administration of appropriate questionnaires at baseline, at the end of the treatment and at one year of follow-up.

1.8.19 Appendix I

Classification of the surgical interventions for breast cancer (FONCaM – Italian Breast Cancer Task Force)

LIMITED BREAST RESECTION: Removal of a small portion of breast tissue including the tumor. Synonyms: tumorectomy, excisional biopsy.

WIDE BREAST RESECTION Removal of a portion of breast tissue including the tumor and a margin of no less than 1 cm of microscopically healthy parenchyma.

QUADRANTECTOMY: Removal of a large section of mammary gland with the overlying skin and the fascia of the large pectoral muscle.

SUBCUTANEOUS MASTECTOMY: Removal of the mammary gland leaving the overlying skin and the nipple-areola complex.

SKIN SPARING MASTECTOMY: Removal of the mammary gland and the nipple-areola complex leaving all or part of the overlying skin.

MASTECTOMY: Total or simple: removal of the mammary gland and of a losenge of overlying skin including areola and nipple. Radical: the term radical is no longer use today since the concept of radicality is considered an objective of either radical surgery or conserving surgery.

FIRST LEVEL AXILLARY DISSECTION: Removal of the lymph nodes laterally at the edge of the small pectoral muscle.

TOTAL AXILLARY DISSECTION: Removal of all the axillary lymph nodes corresponding to the three Berg levels with or without removal of the small pectoral muscle.

1.8.20 Appendix II

INFORMATION FORM FOR THE PATIENT AND ATTENDING PHYSICIAN AND INFORMED CONSENT FOR THE PATIENT

PHASE III STUDY: COMPARISON BETWEEN CONVENTIONAL POST-OPERATIVE RADIOTHERAPY AND PARTIAL AND ACCELERATED IRRADIATION OF THE BREAST WITH THREE DIMENSIONAL CONFORMAL RADIOTHERAPY (3D-CRT) AFTER CONSERVING SURGERY OF THE BREAST TUMOR WITH LOW-RISK OF LOCAL RECURRENCE

Dear Madam,

We propose that you participate in a clinical study promoted by all the Radiotherapy services of the Emilia-Romagna region with the aim of improving knowledge of the effectiveness of the treatments for breast tumors. Your participation is completely voluntary. We ask you to consider your participation in this study taking all the time that you need, and discussing it with family and your family physician if necessary.

WHAT IS THE AIM OF THE STUDY?

The aim of radiotherapy after breast conserving surgery is to reduce the risk of a recurrence of the disease after the surgery. Standard radiotherapy after conserving surgery today is administered for 5-6 weeks. The administration of radiotherapy only on the area of the breast where the neoplasia was located has recently been tried with good results. In these studies different techniques were used, such as interstitial brachytherapy, that consists of the temporary implant of a series of needles or catheters in the cavity of the tumorectomy that is subsequently filled with radioactive material to administer the dose in about 5 days, or endocavity brachytherapy, that consists of placing in the surgical cavity a balloon that is subsequently inflated and in which a radioactive preparation is introduced to administer the dose also in this case in about 5 days.

In other studies, on the other hand, external radiotherapy methods were used with which the radiotherapy is administered only on the area of the breast where the neoplasia was located using a technique called accelerated "three dimensional conformal radiotherapy (3D-CRT)." Accelerated 3D-CRT is a treatment whose effectiveness and safety are still to be demonstrated with certainty; however, it seems to be well tolerated in preliminary studies. This new treatment method proposes to reduce the amount of radiation on healthy tissue, administering the desired dose

of rays on the zone neighboring on that from which your tumor was removed. The total duration of the treatment is 5 days and it is carried out in two daily sessions.

The objective of the study, in which we propose that you participate, is to verify on a large number of patients whether this type of radiotherapy, which involves only part of the breast and has a shorter duration (only 5 days instead of the 25 foreseen by the treatment used today), can give equal results to those of conventional radiotherapy (that administered on the entire breast for a duration of 5-6 weeks) in patients like you who have a disease with low risk of local recurrence. Another important objective of the study is the evaluation of the aesthetic result on the breast undergoing the surgical intervention.

The choice between the traditional method (25 days of treatment) and the short method (5 days of treatment) does not depend on the physicians following you, but will take place according to a completely random method of attribution (randomization) which is a method generally used in controlled clinical studies similar to the study in which we invite you to participate. Only in this way will it be possible to collect reliable data on the equality between the two treatments.

WHAT DOES PARTICIPATION IN THE STUDY INVOLVE?

In the group of patients that receives trial treatment the radiotherapy will be administered on the area from where the tumor was removed twice daily for 5 consecutive working days. The two administrations of the same day will be separated by an interval of 6 hours. In the group of patients that receives the standard treatment, on the other hand, irradiation of the entire breast will be carried out for a total of 5-6 weeks of treatment, one session a day 5 days a week. The radiotherapy in each case must commence within 12 weeks from the surgical intervention, unless chemotherapy is first administered. In the latter case the radiotherapy will commence at least two weeks after administration of the last cycle of chemotherapy. The chemotherapy and radiotherapy can be prescribed in relation to the diameter of the tumor and other risk factors. Your participation in this study in any case will not influence these additional treatments.

If you decide to participate in the study the following examinations and procedures will be prescribed for you:

Prior to entry to the study

Case histories, Mammography, thorax x-ray, Blood chemistry, liver ultrasound/bone scan (based on the indications of your attending physician), breast photograph.

After the treatment

Case history and objective examination (at 6 months and 12 months for the 1st year, every 6 months from the 2nd year to the 5th year, Mammography (annually) Blood chemistry, liver ultrasound, chest x-ray, bone scan (when indicated).

Photographs of the breasts (at 6 and 12 months and then annually).

Evaluation of the aesthetic result (at 6 and 12 months and then annually).

HOW LONG WILL YOU PARTICIPATE IN THE STUDY?

The study provides for the carrying out of the radiotherapy and then the follow-up visits, that will be scheduled every 6 months for the first 3 years than annually for at least 5 years. The physicians participating in the study might ask you to halt the study in your sole interests if in the meantime new scientific information emerges that will allow determination of what the best treatment is. Furthermore, you can decide to suspend your participation in the study at any moment, but we ask you to contact the investigating physician or your attending physician to discuss this decision.

WHAT ARE THE RISKS OF THE STUDY?

The possible side effects during the study are listed below and will be discussed regularly with the investigators or with your attending physician. There might be others that are not foreseeable. Drugs will be dispensed to you that limit all the side effects. The side effects will be basically the same independently of the type of radiotherapy. Probably both with the trial treatment and the traditional treatment most of the side effects will disappear at the end of or shortly after the treatment; it is rare for these to be permanent results. It is also possible that the trial radiotherapy will be less effective or more effective than the standard radiotherapy in controlling and/or preventing recurrence of the tumor.

The side effects listed below can be present in any case independently of the type of radiotherapy treatment carried out.

Probable side effects (concern over 10% of the patients treated)

- Asthenia during the treatment and for a few weeks afterwards;
- Pain and tension in the thoracic muscles of the part treated;
- Reddening of the skin during the treatment and for a few weeks afterwards;

- Slight swelling of the breast;
- The skin in the zone treated may become a little darker, and in some cases it may remain darker indefinitely.

Less probable side effects (3-9% of the patients treated)

- Scaling skin in the area treated
- Pain in the area treated

Rare but important side effects (less than 3% of the patients treated)

- -Cough
- -Respiratory difficulties
- -Inflammation of the pericardium (the membrane surrounding the heart)
- -Inflammation of the heart muscle
- -Fracture of one or several ribs in the part treated

Childbearing Risks

- The effect of the radiation can be harmful for a newborn during breast
- feeding or a fetus in the uterus of the patient undergoing treatment.
- For this reason pregnant or breast-feeding patients are not candidates for participation in the study and for patients of childbearing age non-hormonal contraception is requested.

THERE ARE BENEFITS DERIVING FROM PARTICIPATION IN THE STUDY

If you decide to participate in the study there may or may not be direct benefits for your state of health. The investigators consider that the carrying out of the study can be of benefit for patients affected by breast cancer in the future.

WHAT OTHER POSSIBILITIES OF CHOICE EXIST?

Obviously you can decide not to participate in this study. In this case you will receive the standard breast radiotherapy, the treatment of a 25-day duration.

CONFIDENTIALITY

The physician responsible for the study will request some personal data from you, such as your initials, gender, date of birth, clinical data and possibly other data. This information is important for correct carrying out of the study. This data will be processed in full compliance with Legislative Decree 196 of June 30, 2003 and subsequent modifications and additions, i.e. the personal data protection law. The physician responsible for the study will use your data strictly anonymously and in any case your identity will never be revealed; you will be identified exclusively by a number. Pursuant to the Personal Data Protection Law, the institution responsible for processing of your personal data is the hospital at which the trial it is carried out and the persons responsible are those appointed by that hospital. We inform you that for the Italian or foreign health authorities, it is very important to be able to examine the original clinical files of the patients in order to fulfill the regulations governing clinical trials. Consequently, we ask you to authorize the hospital physician to have the original files examined, only for these purposes, by the qualified personnel of the Health Authorities or the Ethics Committee. You will be entitled at any time to withdraw your authorization for the actions indicated in the preceding point and to suspend your participation in the study; and this will not involve any prejudicial consequences for you. In any case you will have full access, through the hospital physician or your personal physician, to the information concerning you, with the right to exercise as regards this information all rights of cancellation, modification, addition, updating, rectification and blocking within the limits stipulated by Legislative Decree 196 of June 30, 2003 - Protection of Personal Data.

WHAT ARE THE COSTS?

The participation in this study does not involve any additional costs for you. In case of medical problems deriving from the participation in the study assistance is provided without additional costs, but no financial compensation is provided. You will not receive any financial compensation for participation in the study.

WHAT ARE YOUR RIGHTS AS PARTICIPANT?

Participation in this study is voluntary; as already emphasized, you can decide not to participate or leave the study at any moment. Abandoning of the study will not involve penalization of any type. You will be informed of all the developments that might concern your health or influence your desire to continue to participate in the study. By signing the part of this document called "informed consent in writing", you do not lose any legal right.

WHOM CAN YOU CONTACT TO OBTAIN INFORMATION OR SOLVE PROBLEMS THAT MIGHT ARISE IN THE COURSE OF THE STUDY?

Chief investigator or physician delegated by him: Dr.....
Tel :.....

INFORMED CONSENT IN WRITING

I the undersigned declare that I accept the offer to participate in the clinical research study described in this document. My consent is the expression of a free decision, not influenced by promises of economic benefit or of another nature, nor of obligations towards the physician in charge of the study. I am aware that I am free to withdraw from the study at any time I wish, and that I can demand subsequently to be treated by commonly used therapies for the treatment of the disease from which I suffer.

I am aware, furthermore, that I am not obligated to give reasons for my decision to withdraw from the study, unless it derives from the appearance of troubles, undesirable or unforeseen effects. In this case, I undertake from now to inform the physician in charge of the study as soon as possible of the nature and degree of my symptoms.

I have read and understood all the foregoing (paragraph 13, Appendix II), I have formulated questions and received answer on the aspects that were unclear to me. I have had the possibility and the time necessary to consider my participation in the study, to examine this informed consent and to discuss it with other people. I express the consent, also pursuant to Legislative Decree 196 of June 30, 2003 on protection of personal data, so that the data of my clinical files relating to the study are made available by the physician in charge of the study to the qualified personnel of the Health Authorities and the Ethics Committee in total compliance with my rights as explained to me in the information part of this document. I consent in particular that the processing of my personal data, including that relating to the state of health and sexual life, is carried out for the specific purposes of the research

within the limits and by the methods indicated to me in this consent and information document. If I so desire, my family physician, or another physician indicated by me, will be informed of my participation in this study. I confirm that the copy of this information and consent document was delivered to me.

The Patient	Signature	Date
The Legally Recognized Representative(s)	Signature	Date

DECLARATION OF THE INVESTIGATOR

I declare that I have provided the patient with complete information and detailed explanations on the nature, purpose, procedures and duration of this clinical research study. I also declare that I have provided the patient with the information sheet and a dated and signed copy of the Informed Consent form.

SIGNATURE OF THE INVESTIGATOR.....

DATE.....

1.8.21 ANNEX I

QUALITY ASSURANCE PROGRAM OF THE STUDY

The study provides quality control and verification programs (QC) to document the adequacy of the treatments and the data collected, to make the procedures of the different participating centers homogenous as regards the treatments carried out (in toto irradiation of the breast or 3D-CRT partial irradiation and the reporting of the data.

The following are provided:

- Controls for the preliminary accreditation of the institute, in relation to the equipment and procedures;
- Quality controls for definitive accreditation (initial controls) and for the monitoring of the study (random controls).

The centers will be accredited only after evaluation of the technological equipment of the institute and after a quality control of the executive methods of the treatment procedure provided for by the protocol. The documentation relative to the QC is managed by the Coordination Center and analyzed by a group of reviewers.

Controls for the preliminary accreditation of the institute

The participation of the Radiotherapy Center in the study protocol is subject to the availability of adequate technological equipment and sufficient cases for recruitment of the patients (50 recruitable patients a year), deducible from the data declared on the initial information questionnaire attached to the membership sheet. It is also planned for each center to participate in a preliminary dummy run before commencing recruitment of the patients.

The initial information questionnaire will give data relating to: address, telephone details and characteristics of the participating center (University, Hospital, local health unit, private center), number of patients treated/day, number of patients/year recruitable, type of simulator in equipment and simulation method used, TPS in equipment and characteristics of the TPS used for the study, characteristics of the treatment units used and their calibration protocols, availability of backup units, name of the responsible physicians and contact investigators (radiotherapists, physicians, dosimetrists).

The initial quality control with dummy run will evaluate the suitability of the treatment plans drawn up on the basis of the protocol stipulations.

Data will be supplied relating to a reference clinical case with DICOM images of the CT-RT Plan to be used for study of the treatment plan. On the CT scanning, the volumes of interest foreseen by the protocol must be identified and listed and a treatment plan that allows compliance with the dose constraints must be established. The documentation relating to the treatment plan and the data on the dose prescription, calculation of the monitor units, dose-volume histograms (DVH in absolute dose for CTV and OAR) will be sent to the Coordination Center for review.

The following will be evaluated:

1. Data collection sheet for eligibility and randomization
2. Clinical and technical data collection sheet, relating to the patient's characteristics, the pathology and the treatment
3. Printouts of the CT axial images with the marks used (metallic clips) and of the images relating to the dose distributions on the axial, coronal and sagittal sections which include the isocenter (with total plans if boosts are provided for)
4. BEV and DRR of the fields adopted and/or orthogonal for isocenter
5. DVH for the volumes concerned (see above)
6. Output of the TPS in relation to the beams and the irradiation geometries (UM, Energy, beam modifiers, dimensions and angles of incidence of the fields)
7. Documentation relating to the prescriptions and carrying out of the treatment.

Initial quality controls for the definitive accreditation, and random for monitoring of the study

The definitive accreditation of the recruiting center is subject to the controls carried out on its treatments, its procedures and the documentation of the first three randomized patients, for each trial group, for each center.

Controls are planned both for the trial branch of partial breast irradiation (3D-CRT) and for the control branch (conventional RT).

The controls provide for rapid review of the documentation supplied (with request for clarifications and corrections in case of violations of the protocol), followed by an in-depth analysis which excludes the existence of nonconformity (during this phase the center can continue recruitment of the patients). If the controls carried out confirm compliance with the protocol, the participating center will be certified and will be subject to periodic, random controls, on cases selected by the Data Center (1 case for every 30 patients recruited).

The following will be subject to initial and random control (for the standard or partial irradiation):

1. Documents and reports that attest to compliance with the inclusion criteria, the randomization and the correctness of the information reported in the data collection sheets (photographs for toxicity and aesthetic success), including those relating to the medical treatment carried out (for the patients for whom adjuvant treatment is provided), acute and late toxicity observed and the clinical result obtained.

2. CT images used for the treatment plan

3. The paper documentation relating to the prescription, planning of the treatment (dosimetric parameters and parameters of irradiation geometry, dose distributions, DVH, BEV, PDT – total for the boost) and carrying out of the treatment (DRR, x-ray, simulation and portal images, with highlighted GTV and PTV, contention systems used, setup photographs, doses administered, fractions, data relating to the RT sessions and any interval between the fractions).

4. Portal films or paper copy of all the controls carried out during the RT, as also the documentation relating to any modifications of the treatment plan or the course of treatment.

Any deviation from the radiotherapy protocol will be classified on the basis of its criticality.

As regards the controls on the dosimetric data and on the dose distributions the following will be considered major, unacceptable violations:

1. Max. dose that exceeds 120% of the prescribed dose

2. DVH by PTV: 90% of the prescribed dose covers < 90% of the PTV

3. DVH for OAR: data > 5% of the specified value

The following will also be considered major violations:

1. Noncompliance with the eligibility criteria

2. Incomplete data collection sheets as regards data considered indispensable

3. Absence of clips

4. Discrepancy between simulation x-rays or DRR and Portal Images exceeding the limits stipulated by the protocol (> 10 mm, since 10 mm are stipulated between CTV and PTV)

5. Start of the RT beyond the limit allowed by the protocol

6. Prescribed doses administered in a total time > 10 days for PBI and greater than 2 weeks in relation to that stipulated (5 – 7 weeks) for in toto breast irradiation.

The management of the noncompliance will be discussed between the participating centers, the Coordination Center, the data manager and the scientific control committees.

1.8.22 ANNEX II: RTOG Acute and Late Radiation Morbidity Scoring Scheme

RTOG/EORTC Late Radiation Morbidity Scoring Scheme						
ORGAN TISSUE	0	GRADE 1	GRADE 2	GRADE 3	GRADE 4	5
SKIN	None	Slight atrophy; Pigmentation change; Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration	
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; Slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; Field contracture > 10% linear measurement	Necrosis	
MUCOUS MEMBRANE	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia; Little mucous	Marked atrophy with complete dryness; Severe telangiectasia	Ulceration	DE
SALIVARY GLANDS	None	Slight dryness of mouth; Good response on stimulation	Moderate dryness of mouth; Poor response on stimulation	Complete dryness of mouth; No response on stimulation	Fibrosis	AT
SPINAL CORD	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadriplegia	H
BRAIN	None	Mild headache; Slight lethargy	Moderate headache; Great lethargy	Severe headaches; Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; Coma	DIR
EYE	None	Asymptomatic cataract; Minor corneal ulceration or keratitis	Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or glaucoma	Severe keratitis; Severe retinopathy or detachment Severe glaucoma	Panopthalmitis/Blindness	ECE
LARYNX	None	Hoarseness; Slight arytenoid edema	Moderate arytenoid edema; Chondritis	Severe edema; Severe chondritis	Necrosis	TI
LUNG	None	Asymptomatic or mild symptoms (dry cough); Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); Low grade fever; Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; Dense radiographic changes	Severe respiratory insufficiency/continuous O2/Assisted ventilation	YRE
HEART	None	Asymptomatic or mild symptoms; Transient T wave inversion & ST Changes; Sinus tachycardia >110 (at rest)	Moderate angina on effort; Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST changes ; Low QRS	Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; EKG abnormalities	Tamponade/Severe heart failure/Severe constrictive pericarditis	LATED
ESOPHAGUS	None	Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing	Unable to take solid food normally; Swallowing semi-solid food; Dilation may be indicated	Severe fibrosis; Able to swallow only liquids; May have pain on swallowing Dilation required	Necrosis/Perforation Fistula	TO
SMALL/LARGE INTESTINE	None	Mild diarrhea; Mild cramping; Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic; Bowel movement >5 times daily; Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/Perforation Fistula	RADI
LIVER	None	Mild lassitude; Nausea, dyspepsia; Slightly abnormal liver function	Moderate symptoms; Some abnormal liver; function tests; Serum albumin normal	Disabling hepatitic insufficiency; Liver function tests grossly abnormal; Low albumin; Edema or ascites	Necrosis/Hepatic coma or encephalopathy	ATIO

KIDNEY	None	Transient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35 mg %;Creatinine 1.5-2.0 mg %; Creatinine clearance > 75%	Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function; Urea > 36-60mg % Creatinine clearance (50-74%)	Severe albuminuria; Severe hypertension Persistent anemia (< 10%); Severe renal failure; Urea >60 mg% Creatinine >4.0 mg% Creatinine clearance < 50%	Malignant hypotension; Uremic coma/Urea > 100%	**N** E F F E
BLADDER	None	Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)	Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria	Severe frequency & dysuria Severe generalized Telangiectasia (often with petechiae); Frequent hematuria; Reduction in bladder capacity (< 150 cc)	Necrosis/Contracted bladder (capacity < 100 cc); Severe hemorrhagic cystitis	**C T S**
BONE	None	Asymptomatic; No growth retardation; Reduced bone Density	Moderate pain or tenderness; Growth retardation; Irregular bone sclerosis	Severe pain or tenderness; Complete arrest of bone growth; Dense bone sclerosis	Necrosis/Spontaneous fracture	
JOINT	None	Mild joint stiffness; Slight limitation of movement	Moderate stiffness; Intermittent or moderate joint pain; Moderate limitation of movement	Severe joint stiffness; Pain with severe limitation of movement	Necrosis/Complete fixation	

1.9 Result of the study - IRMA

1.9.1 Material and methods

IRMA is an experimental, clinical study of non-inferiority. It is a randomized, controlled, multicenter clinical trial aimed at comparing the partial and accelerated radiation with three-dimensional conformal radiation therapy (3D-CRT) vs. standard radiation therapy following conservative breast surgery (Phase III study) in women at low risk of local relapse treated for breast cancer with conservative surgery.

The primary objective is to assess whether the partial hypofractionated and accelerated 3D-CRT of the surgical cavity only is not inferior to postoperative conventional fractionated radiation of the whole breast in terms of local recurrence, as measured by the incidence of ipsilateral local recurrence as the primary recurrence event.

This study includes 34 clinical sites, of which 23 are Italian and 11 international centers. So far, there have been 2,791 eligible patients, of which 25 patients were excluded and 2766 (83.8) patients were randomized of 3302 expected and included in the current analysis. A total of 1,381 of them were randomized into the partial radiation arm (PBI), and 1,385 into the total radiation arm (WBI).

1.9.2 Statistic analysis

This study is a study of non inferiority, and the dimension of the sample size was planned to include 3,302 patients on the basis of a overall rate in literature between 4% - 7% of local ipsilateral breast recurrences as a first event, within 5 years[17]. Being a non-inferiority study a recurrence rate of 4% was hypothesized for the standard radiation group and a maximum value of the recurrence rate of 6% in the partial radiation group. The type of statistical analysis was chosen according to an “intention to treat”. A thorough descriptive statistical analysis was performed in which data were measured and summarized. A number of statistical tests were performed to observe the differences between the treatment arms. The difference in frequencies were evaluated with both the chi-square test and the Fisher’s exact test, used in cases of low frequencies for categorical variables. Continuous variables were expressed as mean ± standard deviation and range, the average differences were evaluated with the t-test for the two groups, and survival analysis was performed with Kaplan-Meier curves. For the cosmetics results, the weighted Cohen’s Kappa Index was employed, to evaluate the correlation between the radiologist and

the patient. This agreement was Calculated to measure agreement between the radiologist and the patient at the end of treatment, 6 months, 12 months, 24 months and 36 months with the assessment of cosmetics result, using EORTC (Cosmetic Rating System). We used weighted K-Cohen as a measure of agreement because our interest is categorical in 4 categories (cosmetics poor, fair, good and excellent). The selected level of statistical significance is equal to 0.05. All analyzes were performed using the STATA14 statistical package, StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

1.9.3 Result

Between March 2007 and December 2016, 34 clinical centers, 23 Italian and 11 international centers were included. So far, of the 2,791 eligible patients, 25 patients were excluded, and the remaining 2,766 patients were randomized and included in the current analysis. A total of 1,381 were allocated to the partial radiation arm (PBI) and 1,385 to the total radiation arm (WBI) (Figure 1.4). Median follow-up was 3.5 years. Most patients (22.2%) were enrolled from the Bellaria Hospital Center, Bologna, followed by Modena (11.9%), Reggio Emilia (8.7%) and Tilburg (6.6%) (table 1.7). The centers ranked by number of enrolled patients are presented in Figure 1.5. Median follow-up and 3.2 years. The cumulative enrollment shows an increasing trend, but between the lines of actual and anticipated enrollment remain separate because the actual enrollment is lower than expected (Figure 1.6). The results showed that the average age between the treatment arms were similar, 64.4 and 64 years respectively; also the subdivision into age groups showed a homogeneity between the treatment arms. Over 70% of the patients are under 70 years old. The histology and TNM classes are balanced between the two treatment arms. Most patients were classified as T1N0 (81%); only 33% of patients had tumors less than 1 centimeter and 91% of patients were classification N0. Over 90% of patients registered ER+ hormone receptors, and over 80% registered PR +. A total of 10% received chemotherapy and more than 56% received hormone therapy (Table 1.8). No statistical significance (p>0.05) was found, confirming homogeneity between the two treatment arms. Of the patients prescribed hormonal therapy, over 40% were prescribed IA and 14% TAM. Of the 10% of patients treated with chemotherapy, 6% received Antracicline and 3% Taxani (Table 1.9). No statistically significant (p> 0.05) was found between the groups. These data confirm a balance between the treatment arms. The toxicity was assessed using the National Cancer

Institute Common Toxicity Criteria for adverse events. A total of 48% of women reported acute toxicity, as measured immediately following treatment; in the PBI arm toxicity was 34% and in the WBI it was 63%. A statistically significant difference was found between the two groups, p <0.001. No high grade skin toxicity was observed (table 1.10). A single incidence of grade 1 acute pulmonary toxicity occurred (in the WBI arm), and a single incidence of grade 2 heart toxicity was registered (in the WBI arm). Also for late skin based toxicity, the WBI arm registered a higher incidence compared to the PBI arm (35% vs. 41%), resulting in a statistically significant difference (p = 0.005). Again, in terms of pulmonary toxicity, a higher percentage in the WBI arm (Grade 1 and 2) was observed compared to only 1 case in the PBI arm (grade 3); 0.9% vs. 1.4%, but statistical significance was not achieved, p = 0.333. However, the situation is reversed when considering late heart toxicity, where in the PBI arm 2 cases (grade 3 and 4) were reported. The percentages for the WBI vs PBI of 0.4% vs 0.1% were not statistically significant p = 0.187. Similarly, late bone toxicity was more frequent in the PBI arm, 12 cases of grade 3 and 4, resulting in 2% for the PBI arm vs. 0.4% for the WBI arm; but this difference was not statistically significant, p = 0.065. For soft tissues grade 3 toxicities were registered in both the arms, whereas grade 4 was only registered in the PBI arm, p <0.001. Finally, other toxicity of grade 3 and 4 were found to be similar between the two arms, p = 0.556 (Table 1.11). The PBI groups therefore registered less skin toxicity but more toxicity in the soft tissues. The follow-up is still relatively early, patients continue to be followed to determine whether differences in bad cosmetics and toxicity will increase over time. The Kaplan - Meier curves was performed for the primary and secondary end-points for patients enrolled up to December 2016. A total of 10 (0.4%) patients registered local, ipsilateral recurrence (Table 1.12). The local, ipsilateral recurrence-free survival was 99% at 5 years (Figure 1.7). The locoregional recurrences are 5 (0.2%) the interested sites are axillary followed by supraclavicular (Figure 1.8). The distant recurrences are 23 (0.8%) in 41 (1.5%) patients with tumors (Figure 1.9) the most interesting site is bone followed by lung, brain and liver. Cosmetics was assessed according to IRMA protocol parameters. The analysis of the correlation for cosmetics between the radiologist and the patient was assessed by using the inter-rater agreement method of K-Cohen index. The value of K at the end of treatment is 0.73 that is a good agreement between the radiologists and the patients, even at 6, 12, 24 and 36 months and confirmed this agreement with K values to be in range 0.66 to 0.70, the interpretation of K is good agreement (Tables 1.13-1.17).

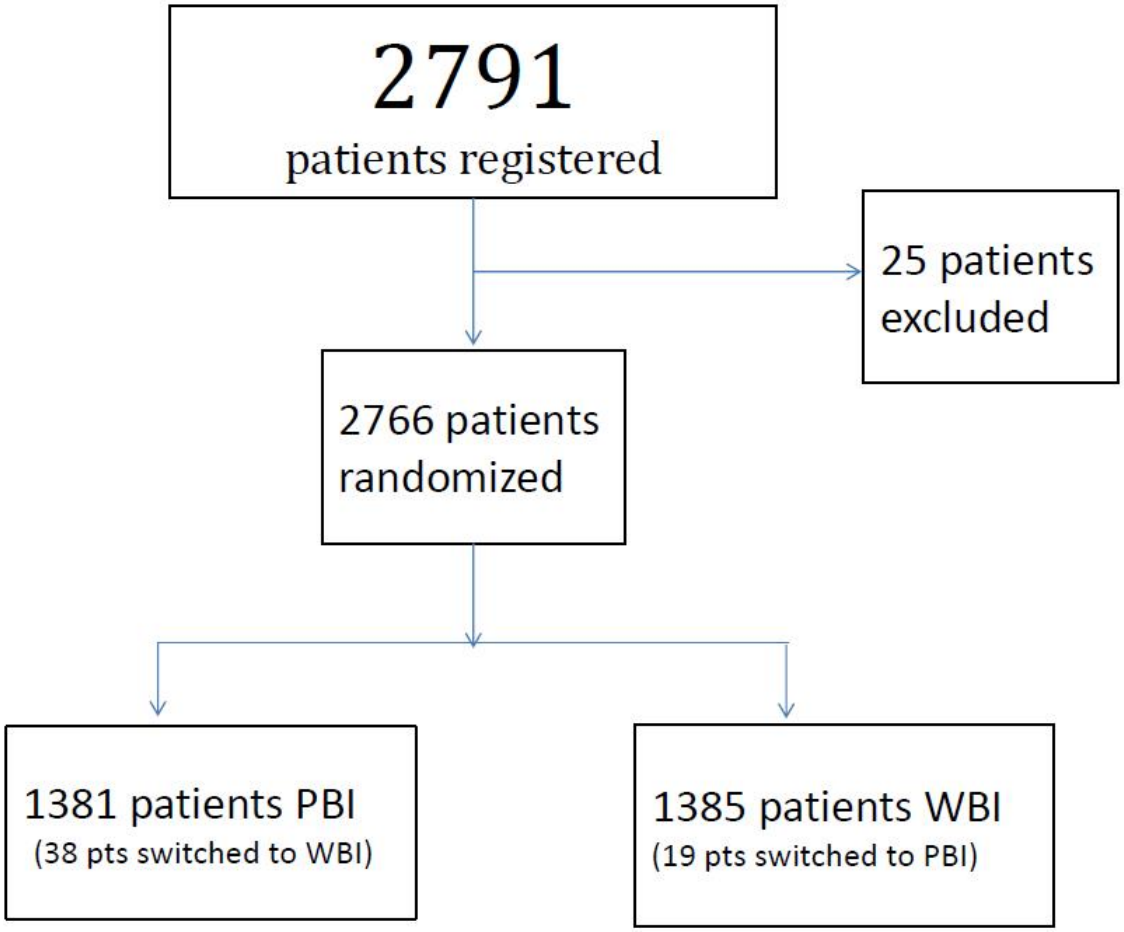

Figure 1.4: Flowchart

Number	Center	PBI		WBI		Total	
		N.	%	N.	%	N.	%
6	Bologna Ospedale Bellaria	303	21.9	310	22.4	613	22.2
1	Modena	153	11.1	176	12.7	329	11.9
2	Reggio Emilia	119	8.6	123	8.9	242	8.7
24	Tilburg	96	7.0	86	6.2	182	6.6
16	San Giovani Rotondo	53	3.8	63	4.5	116	4.2
25	Maastricht	59	4.3	55	4.0	114	4.1
27	Enschede	51	3.7	61	4.4	112	4.0
22	Bellinzona	53	3.8	47	3.4	100	3.6
32	Arnhem	54	3.9	44	3.2	98	3.5
11	Como	43	3.1	43	3.1	86	3.1
10	Bologna A.O. pol. S. Orsola	34	2.5	35	2.5	69	2.5
34	Groningen	29	2.1	31	2.2	60	2.2
8	Ravenna	33	2.4	26	1.9	59	2.1
5	Piacenza	33	2.4	20	1.4	53	1.9
18	Haifa	23	1.7	22	1.6	45	1.6
31	Deventer	24	1.7	21	1.5	45	1.6
9	Bologna Univ. Policlinico-S. Orsola	22	1.6	20	1.4	42	1.5
26	Pavia	23	1.7	19	1.4	42	1.5
30	Valencia	18	1.3	21	1.5	39	1.4
14	Roma	17	1.2	21	1.5	38	1.4
35	Amsterdam	20	1.4	17	1.2	37	1.3
3	Rimini	21	1.5	15	1.1	36	1.3
20	Treviglio	17	1.2	14	1.0	31	1.1
28	Varese	16	1.2	14	1.0	30	1.1
23	Torino	16	1.2	13	0.9	29	1.0
7	Ferrara	9	0.7	19	1.4	28	1.0
13	Ancona	10	0.7	12	0.9	22	0.8
12	Cotignola	11	0.8	8	0.6	19	0.7
21	Castellanza	7	0.5	8	0.6	15	0.5
36	Nijmege	5	0.4	10	0.7	15	0.5
4	Parma	4	0.3	7	0.5	11	0.4
29	Bergamo	4	0.3	3	0.2	7	0.3
17	Genova	1	0.1	0	0.0	1	0.0
19	Meldola	0	0.0	1	0.1	1	0.0
	Total	**1381**	**100**	**1385**	**100**	**2766**	**100**

Table 1.7: Patients recruitment by center

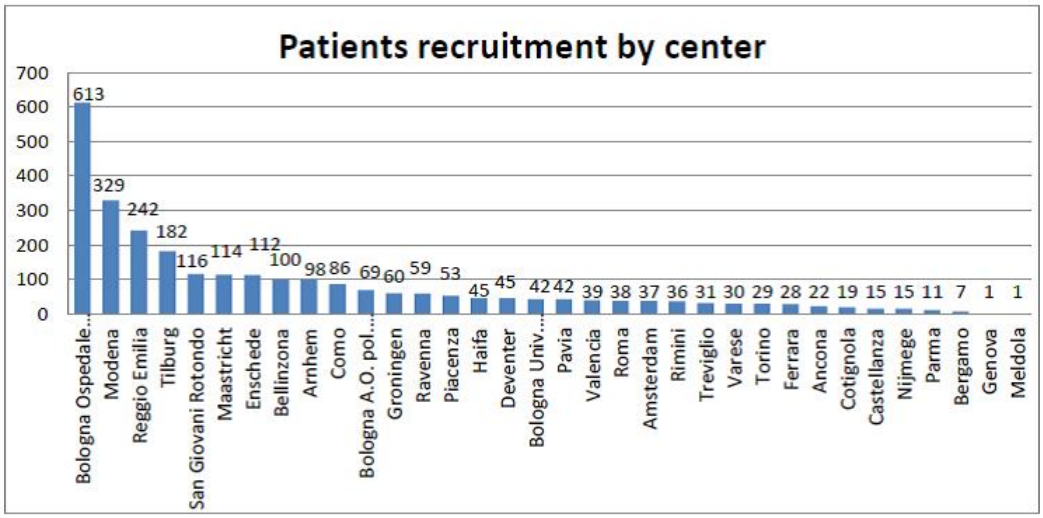

Figure 1.5: Patients recruitment by center

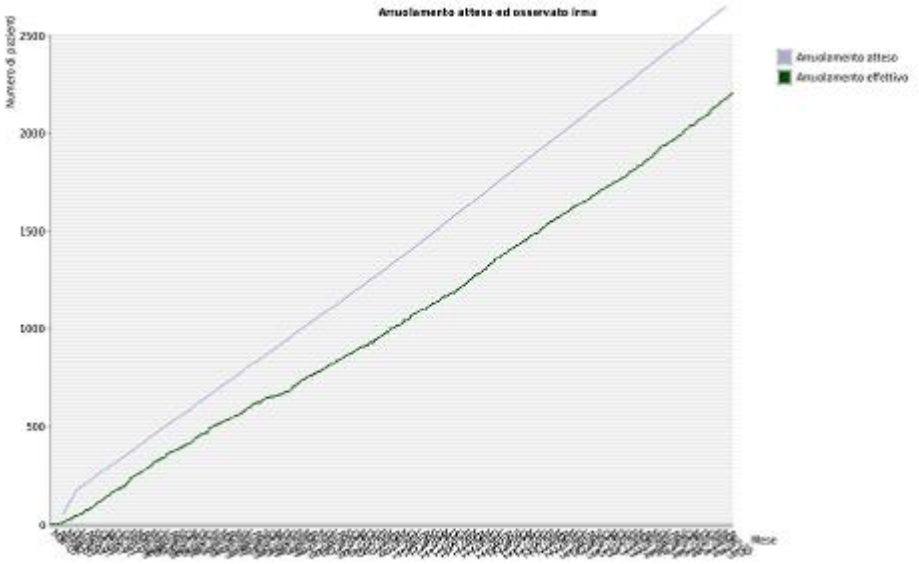

Figure 1.6: Patients recruitment by center

Characteristics		PBI		WBI		OVERALL	
		N.	%	N.	%	N.	%
	Randomized	1381		1385		2766	
Age (at randomization)							
	49-60	425	30.8%	441	31.8%	866	31.3%
	60-70	611	44.2%	564	40.7%	1175	42.5%
	70+	345	25.0%	380	27.4%	725	26.2%
	Mean age ±SD (min-max)	64.4 ±8.0 (49-90)		64.6 ±8.3 (49-87)		64.5 ±8.1 (49-90)	
Histology							
	Ductal	1125	81.5%	1130	81.6%	2255	81.5%
	Lobular	132	9.6%	121	8.7%	253	9.1%
	Other	53	3.8%	49	3.5%	102	3.7%
	NOS	17	1.2%	26	1.9%	43	1.6%
	Missing	54	3.9%	59	4.3%	113	4.1%
TNM classes							
	T1N0	1133	82.0%	1122	81.0%	2255	81.5%
	T2N0	77	5.6%	96	6.9%	173	6.3%
	T1N1	97	7.0%	87	6.3%	184	6.7%
	T2N1	14	1.0%	14	1.0%	28	1.0%
	Missing	60	4.3%	66	4.8%	126	4.6%
T size							
	<1 cm	459	33.2%	464	33.5%	923	33.4%
	>=1 cm	922	66.8%	921	66.5%	1843	66.6%
lymph nodes status							
	N0	1266	91.7%	1273	91.9%	2539	91.8%
	N1	115	8.3%	112	8.1%	227	8.2%
Hormonal receptors							
	ER+	1265	91.60%	1253	90.5%	2518	91.0%
	ER-	52	3.8%	64	4.6%	116	4.2%
	ERx	1	0.1%	0	0.0%	1	0.0%
	Missing	63	4.6%	68	4.9%	131	4.7%
	PR+	1112	80.5%	1121	80.9%	2233	80.7%
	PR-	200	14.5%	195	14.1%	395	14.3%
	PRx	1	0.1%	0	0.0%	1	0.0%
	Missing	68	4.9%	69	5.0%	137	5.0%
Adjuvant therapies							
	None	386	28.0%	390	28.2%	776	28.1%
	chemotherapy	151	10.9%	140	10.1%	291	10.5%
	Hormonal therapy	785	56.8%	791	57.1%	1576	57.0%
	Missing	59	4.3%	64	4.6%	123	4.4%

Table 1.8: Characteristics of randomized patients

		PBI		WBI		OVERALL	
		N.	%	N.	%	N.	%
	Randomized	1381		1385		2766	
Hormonal Therapies							
	No	537	39%	530	38%	1067	39%
	Yes	785	57%	791	57%	1576	57%
	Missing	59	4%	64	5%	123	4%
Hormonal Therapies							
TAM	No	1109	80%	1147	83%	2256	82%
	Yes	213	15%	174	13%	387	14%
	Missing	59	4%	64	5%	123	4%
IA	No	756	55%	709	51%	1465	53%
	Yes	566	41%	612	44%	1178	43%
	Missing	59	4%	64	5%	123	4%
LR-HR	No	1276	92%	1297	94%	2573	93%
	Yes	46	3%	24	2%	70	3%
	Missing	59	4%	64	5%	123	4%
OTHER	No	1317	95%	1318	95%	2635	95%
	Yes	5	0%	3	0%	8	0%
	Missing	59	4%	64	5%	123	4%
TOTAL	No	4458	323%	4471	323%	8929	323%
	Yes	830	60%	813	59%	1643	59%
	Missing	236	17%	256	18%	492	18%
Chemotherapy							
	No	1171	85%	1181	85%	2352	85%
	Yes	151	11%	140	10%	291	11%
	Missing	59	4%	64	5%	123	4%
Chemotherapy							
CMF	No	1312	95%	1304	94%	2616	95%
	Yes	10	1%	17	1%	27	1%
	Missing	59	4%	64	5%	123	4%
Antracicline	No	1232	89%	1235	89%	2467	89%
	Yes	90	7%	86	6%	176	6%
	Missing	59	4%	64	5%	123	4%
Taxani	No	1278	93%	1278	92%	2556	92%
	Yes	44	3%	43	3%	87	3%
	Missing	59	4%	64	5%	123	4%
Herceptin	No	1307	95%	1306	94%	2613	94%
	Yes	15	1%	15	1%	30	1%
	Missing	59	4%	64	5%	123	4%
Other	No	1291	93%	1290	93%	2581	93%
	Yes	31	2%	31	2%	62	2%
	Missing	59	4%	64	5%	123	4%

Table 1.9: Systemic treatment characteristics

Acute toxicities	PBI	%	WBI	%	Total	%
Missing	111	8,038	114	8,231	225	8,13
No	800	57,93	387	27,94	1187	42,91
Yes	470	34,03	884	63,83	1354	48,95
Total	1381	100	1385	100	2766	100

Table 1.10: Acute toxicities

		PBI		WBI		Total	
		N.	%	N.	%	N.	%
	Randomized	1381		1385		2766	
Skin							
	None	878	63.6	789	57.0	1667	60.3
	1	427	30.9	508	36.7	935	33.8
Grade	2	69	5.0	80	5.8	149	5.4
	3	7	0.5	8	0.6	15	0.5
	4	0	0.0	0	0.0	0	0.0
Lung							
	None	1369	99.1	1366	98.6	2735	98.9
	1	8	0.6	16	1.2	24	0.9
Grade	2	3	0.2	3	0.2	6	0.2
	3	1	0.1	0	0.0	1	0.0
	4	0	0.0	0	0.0	0	0.0
Heart							
	None	1376	99.6	1383	99.9	2759	99.7
	1	1	0.1	2	0.1	3	0.1
Grade	2	2	0.1	0	0.0	2	0.1
	3	1	0.1	0	0.0	1	0.0
	4	1	0.1	0	0.0	1	0.0
Bone							
	None	1353	98.0	1379	99.6	2732	98.8
	1	5	0.4	4	0.3	9	0.3
Grade	2	10	0.7	2	0.1	12	0.4
	3	2	0.1	0	0.0	2	0.1
	4	11	0.8	0	0.0	11	0.4
Soft tissues							
	None	653	47.3	706	51.0	1359	49.1
	1	458	33.2	493	35.6	951	34.4
Grade	2	247	17.9	175	12.6	422	15.3
	3	22	1.6	11	0.8	33	1.2
	4	1	0.1	0	0.0	1	0.0
Other							
	None	1302	94.3	1329	96.0	2631	95.1
	1	60	4.3	45	3.2	105	3.8
Grade	2	17	1.2	9	0.6	26	0.9
	3	2	0.1	1	0.1	2	0.1
	4	0	0.0	1	0.1	1	0.0
Total							
	None	6931	83.6	6952	83.7	13883	83.7
	1	959	11.6	1068	12.9	2027	12.2
Grade	2	348	4.2	269	3.2	617	3.7
	3	35	0.4	19	0.2	54	0.3
	4	13	0.2	1	0.0	14	0.1

Table 1.11: Late toxicities

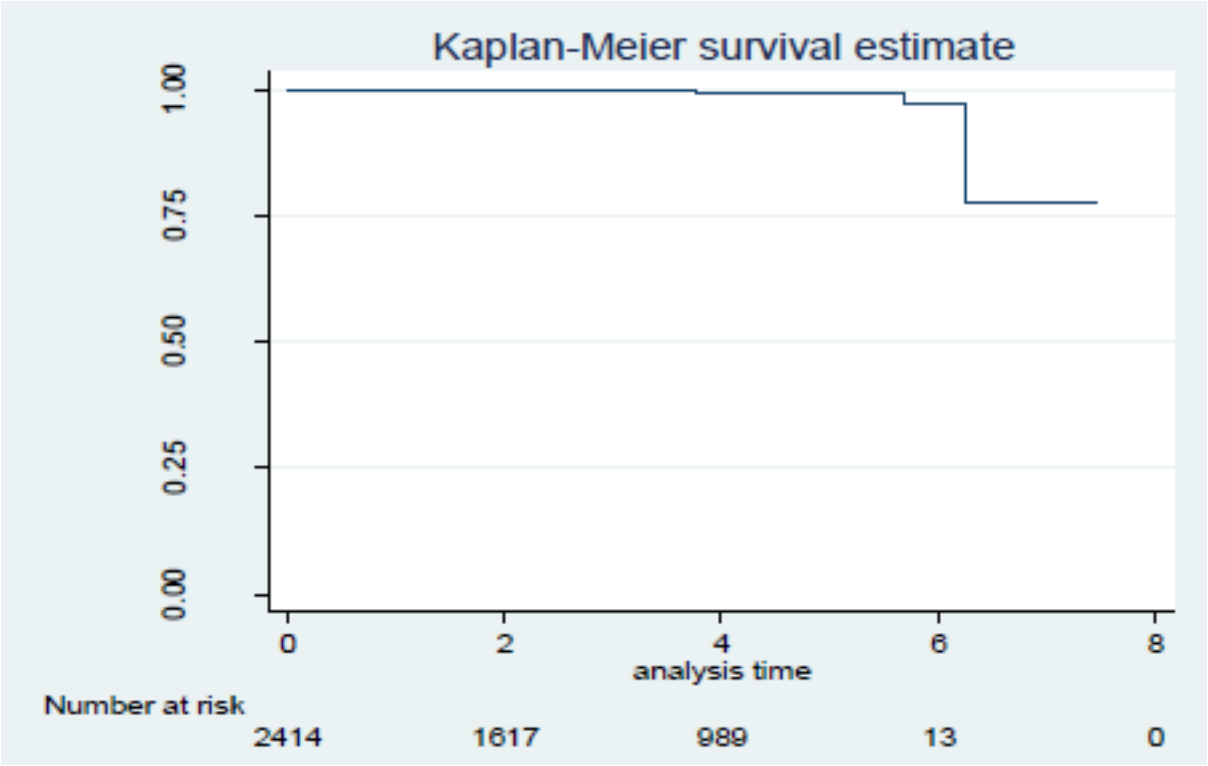

Figure 1.7: Survival analysis, local recurrences

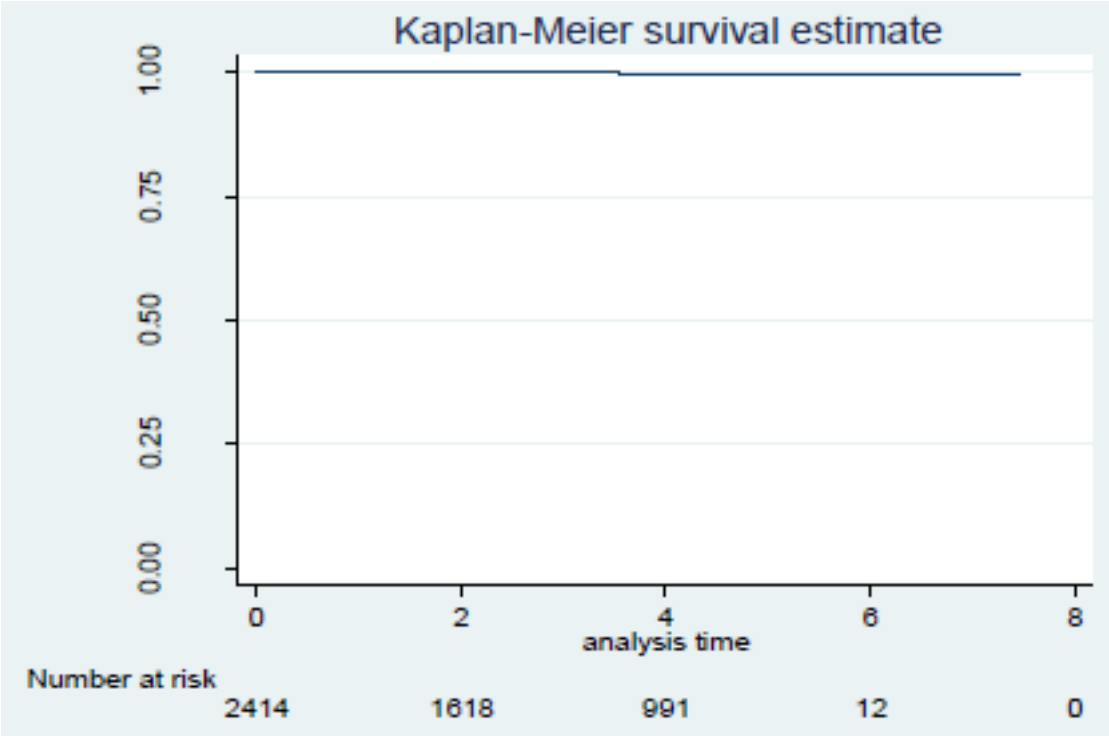

Figure 1.8: Survival analysis, locoregional recurrences

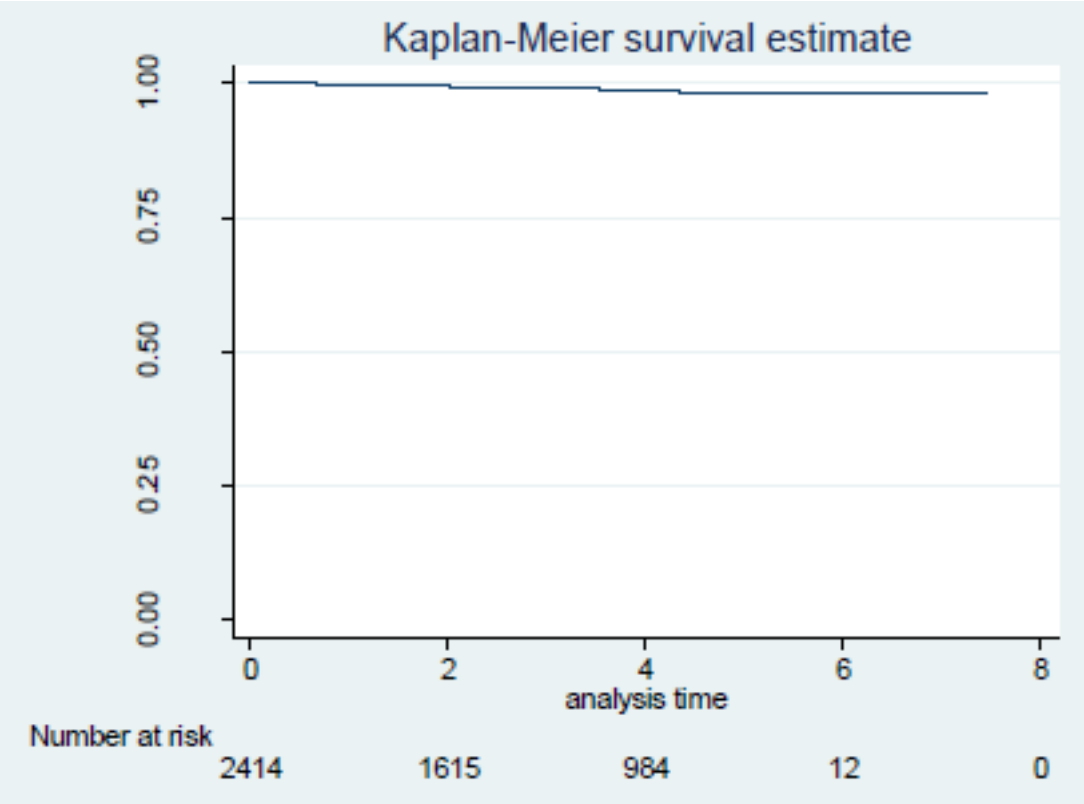

Figure 1.9: Survival analysis, distant recurrences

		Total	
		N.	%
	Randomized	2766	
Local recurrences			
	No	2756	99.6
	Yes	10	0.4
Site of local recurrences		0	0.0
	Tumor site	5	0.2
	Other quadrant	6	0.2
	Total	11	0.4
Locoregional recurrences			
	No	2761	99.8
	Yes	5	0.2
Site of locoregional recurrences			
	Axillary	4	0.1
	Supraclavicular	2	0.1
	Internal mammary	0	0.0
	Infraclavicular	1	0.0
	Total	7	0.3
Distant recurrences			
	No	2743	99.2
	Yes	23	0.8
Site of distant recurrences			
	Lung	9	0.3
	Liver	6	0.2
	Bone	15	0.5
	Brain	5	0.2
	Lymphonodes	4	0.1
	Skin	0	0.0
	Other	2	0.1
	Total	41	1.5

Table 1.12: Recurrences by site

	End of treatment	Assessment of radiologist				
		Poor	Fair	Good	Excellent	
Assessment patients	Poor	13	9	0	0	22 (1.3%)
	Fair	17	161	45	1	224 (13.3%)
	Good	2	54	1009	38	1103 (65.7%)
	Excellent	0	3	63	263	329 (19.6%)
		32 (1.9%)	227 (13.5%)	1117 (66.6%)	302 (18.0%)	1678
	Weighted Kappa[a]	0.731				
	Standard error	0.017				
	95% CI	0.69 to 0.76				

[a] Linear weights

Table 1.13: Agreement between radiologist and patients, end of treatment

	Follow up 6 month	Assessment of radiologist				
		Poor	Fair	Good	Excellent	
Assessment patients	Poor	23	12	8	0	43 (2.4%)
	Fair	18	130	30	4	182 (10.3%)
	Good	6	66	940	70	1082 (61.1%)
	Excellent	0	11	79	375	465 (26.2%)
		47 (2.7%)	219 (12.4%)	1057 (59.7%)	449 (25.3%)	1772
	Weighted Kappa[a]	0.691				
	Standard error	0.017				
	95% CI	0.65 to 0.72				

[a] Linear weights

Table 1.14: Agreement between radiologist and patients, 6 month

	Follow up 12 month	Assessment of radiologist				
		Poor	Fair	Good	Excellent	
Assessment patients	Poor	20	8	3	1	32 (1.9%)
	Fair	17	118	33	4	172 (10.3%)
	Good	8	73	871	60	1012 (60.5%)
	Excellent	0	12	74	371	457 (27.3%)
		45 (2.7%)	211 (12.6%)	981 (58.6%)	436 (26.1%)	1673
	Weighted Kappa[a]	0.698				
	Standard error	0.017				
	95% CI	0.65 to 0.73				

[a] Linear weights

Table 1.15: Agreement between radiologist and patients, 12 month

	Follow up 24 month	Assessment of radiologist				
		Poor	Fair	Good	Excellent	
Assessment patients	Poor	17	6	2	2	27 (2.1%)
	Fair	8	89	15	3	115 (9.0%)
	Good	9	71	648	44	772 (60.4%)
	Excellent	0	3	61	300	364 (28.5%)
		34 (2.7%)	169 (13.2%)	726 (56.8%)	349 (27.3%)	1278
	Weighted Kappa[a]	0.701				
	Standard error	0.017				
	95% CI	0.66 to 0.73				

[a] Linear weights

Table 1.16: Agreement between radiologist and patients, 24 month

	Follow up 36 month	Assessment of radiologist				
		Poor	Fair	Good	Excellent	
Assessment patients	Poor	22	6	0	0	28 (2.5%)
	Fair	10	84	13	1	108 (9.7%)
	Good	12	50	582	47	691 (62.1%)
	Excellent	0	5	61	220	286 (25.7%)
		44 (4.0%)	145 (13.0%)	656 (58.9%)	268 (24.1%)	1113
	Weighted Kappa[a]	0.665				
	Standard error	0.022				
	95% CI	0.62 to 0.71				

[a] Linear weights

Table 1.17: Agreement between radiologist and patients, 36 month

1.10 Conclusion

In conclusion, the results of IRMA trial are presented confirming that randomization has worked since the two groups are well balanced in terms of prognostic factors. The length of follow-up is still relatively early, therefore patients will continue to be followed up to determine whether differences in bad cosmetics and toxicity will increase over time.

The study was planned to enroll 3302 patient, so far 2766 of them have been recruited (84%). On average 30 patients per month are enrolled and we expect to reach the plane sample size in one and half years.

Since the study is still enrolling patients can only present preliminary result and cannot provide final statement about the efficacy and safety of treatments under comparison.

However, the data so far analyzed suggest that the two groups are comparable in terms of baseline characteristics, that the quality of data is satisfactory and overall results are in line with expected ones.

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Chapter 2

Title: Prevalence and diagnosis of vestibular disorders in children: A review

Authors: Federico Maria Gioacchini, Matteo Alicandri-Ciufelli, Shaniko Kaleci, Giuseppe Magliulo, Massimo Re.

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2.1 Abstract

Objectives: To systematically review and discuss the main pathologies associated with vertigo and dizziness in children, paying particular attention to recent advances in diagnosis and therapy.

Methods: One appropriate string was run on PubMed to retrieve articles dealing with the topics mentioned above. A cross-check was performed on citations and full-text articles found using the selected inclusion and exclusion criteria. A non-comparative meta-analysis concerning the rate of singular vertiginous forms was performed.

Results: Ten articles were identified comprising a total of 724 subjects. Overall, the articles we analyzed indicated benign paroxysmal vertigo of childhood (18.7%) and migraine-associated vertigo (17.6%) as the two main entities connected with vertigo and dizziness in children. Head trauma (14%) was the third most common cause of vertigo. The mean (95% CI) rate of every vertiginous form was also cal-

culated in relation to the nine studies analyzed with vestibular migraine (27.82%), benign paroxysmal vertigo (15.68%) and vestibular neuritis (9.81%) being the three most common forms. There appeared to be a paucity of recent literature concerning the development of new diagnostic methods and therapies.

Conclusions: On the basis of the literature study, when evaluating a young patient with vertigo and dizziness, the otolaryngologist should be aware that, in children, these symptoms are often connected to different pathologies in comparison to the entities observed in the adult population.

2.2 Introduction

Episodic vertigo and dizziness are less frequent symptoms in children than in the adult population and have been studied less extensively. The prevalence of vestibular disorders in the pediatric population ranges between 0.7% and 15%, with the higher values obtained from studies using a patient questionnaire as the primary method of data collection[1–3].

In their retrospective review of 561,151 patients, O'Reilly et al.[4] found a cumulative prevalence of diagnosis related to a balance of 0.45% (2546/561,151). Between these 2546 patients, only 159 were diagnosed with a clearly defined peripheral vestibular pathology while the majority of them were considered affected by an "unspecified peripheral vertigo".

If vertigo is present in a child, various peripheral and central vestibular syndromes may be implicated and exhaustive clinical and laboratory work-up is needed to obtain a correct diagnosis[5].

Nevertheless, despite the most significant technological achievements in the development of diagnostic tools since then, diagnosis is still based mainly upon the patient's history and physical examination. Moreover, the differential diagnosis of childhood vertigo differs from that of adults because several etiologies are unique to the pediatric population while the occurrences of other pathologies are rather different in children and adults[6].

The predominant forms of vertigo in children are benign paroxysmal vertigo of childhood (BPV), vestibular migraine (VM), and otitis media (OM)/middle ear effusion (MEE)-related dizziness[1].

Analyzing the more recent articles focusing on this topic, the aim of this review was to define and discuss the main clinical entities causing vestibular symptoms

during childhood.

2.3 Material and methods

In July 2013, a literature search was performed using the following search string on PubMed:

- "Child"[Mesh] AND "Vertigo"[Mesh] OR "Dizziness"[Mesh].

The initial search returned a total of 4165 results. Abstracts and titles obtained were screened independently by two of the authors (FMG and MR) who subsequently met and discussed disagreements on citation inclusion.

Concerning the rate of singular vertiginous forms, we performed a non-comparative meta-analysis and the betweenstudy heterogeneity was assessed with the χ^2-based Cochran's Q statistic test and I^2 metric. Heterogeneity was considered significant at $P < 0.01$ for the Q statistic (to assess whether observed variance exceeded expected variance). For the I^2 metric (I^2 = 100% (Q df)/Q), the following cut-off points were used: I^2 = 0–25%, no heterogeneity; I^2 = 25–50%, moderate heterogeneity; I^2 = 50–75%, large heterogeneity; I^2 = 75–100%, extreme heterogeneity. All analyses were performed with the statistical package STATA12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

2.4 Results

After an initial check, full-text retrieval, and manual crosschecking of references included in the articles, nine studies comprising a total of 724 subjects were chosen for analysis. The characteristics of these selected studies are included in Table 2.1. A further study, in which more than 2000 patients were analyzed, is also reported in Table 2.1 although the authors of this article only indicated the percentage incidence of each pathology.

	n	Mean ages	Migraine	BPV	Vestibular neuritis	Meniere's disease	BPPV	Psychogenic vertigo	MEE/OM	Head trauma	Orthostatic hypotension
Bower and Cotton [2]	34	10.6	4 (12%)	5 (15%)	3 (9%)	2 (6%)	0	0	5 (15%)	3 (9%)	0
D'Agostino et al. [31]	282	N/A	15 (5%)	60 (21%)	3 (1%)	0	0	0	x	85 (30%)	0
Weisleder and Fife [13]	31	13	11 (35%)	6 (19%)	0	2 (6%)	0	3 (10%)	0	0	0
Ravid et al. [46]	62	11.8	24 (39%)	10 (16%)	9 (14%)	0	0	8 (13%)	x	2 (3%)	5 (9%)
Choung et al. [25]	55	11.8	17 (31%)	14 (25%)	1 (2%)	2 (4%)	2 (4%)	0	x	4 (7%)	0
Riina et al. [1]	119	10.9	17 (14%)	23 (19%)	14 (12%)	2 (2%)	1 (1%)	6 (5%)	12 (10%)	6 (5%)	4 (3%)
Erbek et al. [47]	50	11.5	17 (34%)	6 (12%)	2 (4%)	1 (2%)	6 (12%)	5 (10%)	x	0	0
Balatsouras et al. [5]	54	8.9	11 (20%)	9 (17%)	15 (28%)	1 (2%)	4 (7%)	0	5 (9%)	3 (5%)	0
Gruber et al. [6]	37	14	12 (32%)	3 (8%)	8 (22%)	1 (3%)	0	8 (22%)	x	1 (3%)	0
Total subjects	724		128 (17.6%)	136 (18.7%)	55 (7.6%)	11 (1.5%)	13 (1.8%)	30 (4.1%)	22 (3%)	104 (14%)	9 (1.2%)
Wiener-Vacher [48]	>2000	N/A	25%	20%	5%	N/A	N/A	N/A	N/A	10%	N/A

BVP: benign paroxysmal vertigo; BPPV: benign paroxysmal positional vertigo; MEE: middle ear effusion; OM: otitis media; N/A: not available. Some studies excluded children with otitis media (denoted with x).

Table 2.1: Literature reports of the most common causes of vertigo/dizziness in children.

Between the 724 subjects grouped in this review, the most commonly diagnosed pathologies were benign paroxysmal vertigo and VM with rates of 18.7% and 17.6%, respectively. Head trauma with a rate of 14% was the third most common cause of vertigo.

Concerning middle ear effusion, it must be noted that this entity was not considered by many authors of the studies analyzed in our review. This observation suggests that the rate of middle ear effusion and otitis media causing vertigo (3%) is highly underestimated in our review.

Overall, psychogenic vertigo accounted for 4.1% of all cases while benign paroxysmal positional vertigo (BPPV; 1.8%), Me´ nie‘ re's disease (1.5%) and orthostatic hypotension (1.2%) were rarer causes of vertigo in children.

The audiometric examinations with the different vestibular tests performed in the analyzed studies were summarized in Table 2.2.

	Audiometric examination		Vestibular tests performed
	Normal	Abnormal	
Bower and Cotton [2]	26 (79%)[a]	7 (21%)[a]	Electronystagmography
D'Agostino et al. [31]	N/A	N/A	N/A
Weisleder and Fife [13]	N/A	N/A	N/A
Ravid et al. [46]	N/A	N/A	Electronystagmography
Choung et al. [25]	42 (76%)	13 (24%)	Electronystagmography Positional/positioning test Caloric test Rotation chair test
Riina et al. [1]	92 (81%)[*]	22 (19%)[*]	Electronystagmography Dix-Hallpike test
Erbek et al. [47]	47 (94%)	3 (6%)	Electronystagmography Tracking test Optokinetic test Dix-Hallpike test Caloric test
Balatsouras et al. [5]	39 (72%)	15 (28%)	Electronystagmography Dix-Hallpike test Optokinetic test Caloric test
Gruber et al. [6]	27 (73%)	10 (27%)	Caloric test
Wiener-Vacher [48]	N/A	N/A	N/A

[a] Audiogram unavailable for one child.
[*] Audiogram unavailable for five children.
N/A: not available.

Table 2.2: Audiometric examination and vestibular tests performed in the analyzed studies.

The mean (95% CI) rate of every vertiginous form was calculated in relation to the nine studies analyzed. This gave, respectively, 27.82% for VM (Fig. 2.1), 15.68% for benign paroxysmal vertigo (Fig. 2.2), 9.81% for vestibular neuritis, 4.08% for Me´ nie‘ re's disease, 2.12% for BPPV, 8.28% for psychogenic vertigo, 4.1% for middle ear effusion and otitis media, 3.82% for head trauma, and 0.58% for orthostatic hypotension.

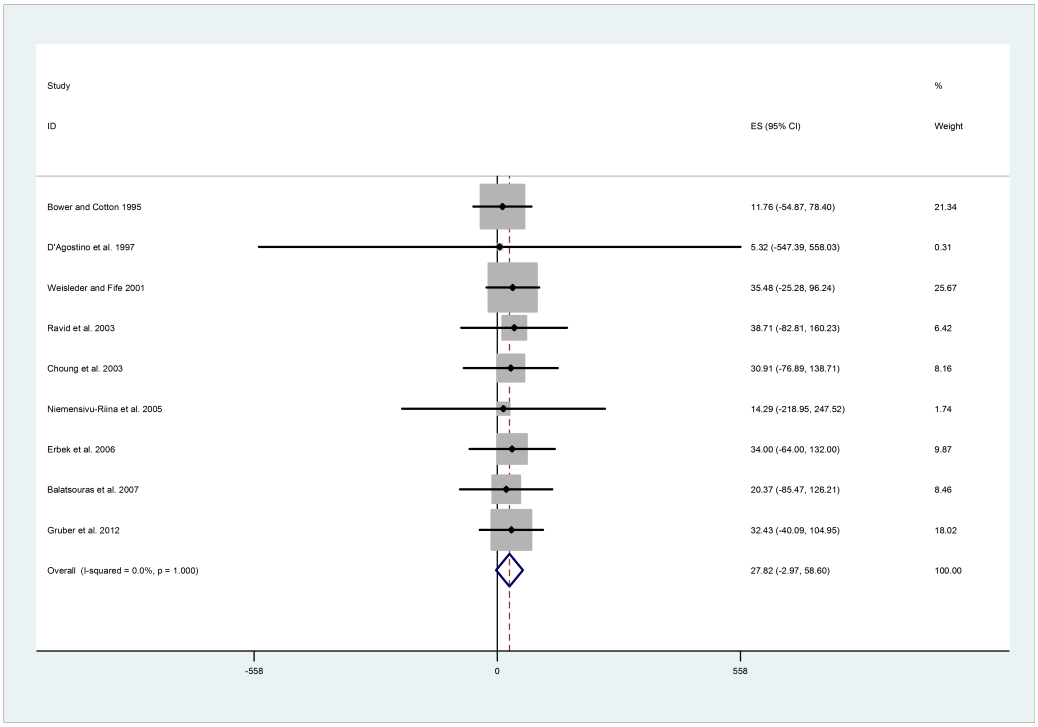

Figure 2.1: Rate of migraine vertigo. Square represent percentage point estimates and horizontal lines represent 95% CIs.

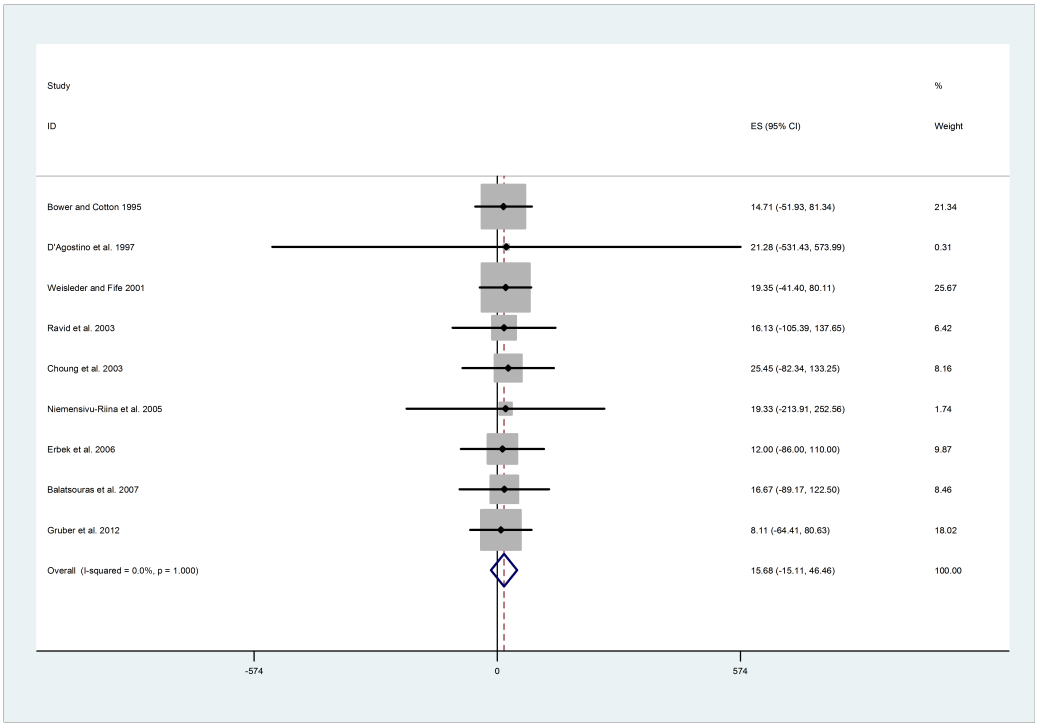

Figure 2.2: Rate of BPV. Square represent percentage point estimates and horizontal lines represent 95% CIs.

On the basis of the literature analyzed in our study, we have proposed an algorithm comprising the main pathological entities that should be suspected in a child presenting with vertigo or dizziness (Fig. 2.3).

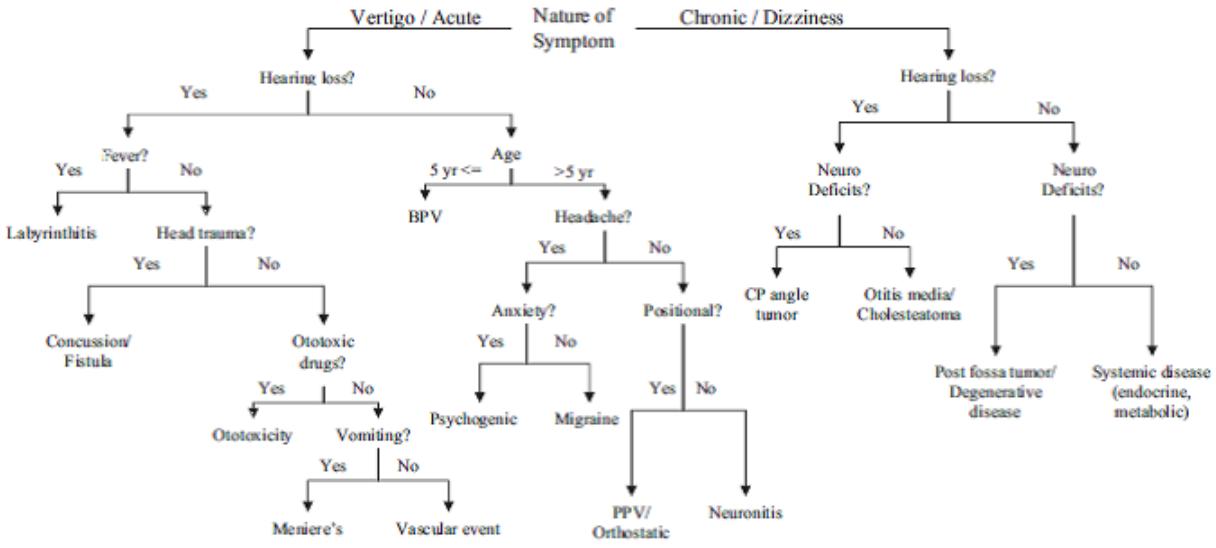

Figure 2.3: Algorithm summarizing the main differential diagnosis of vertigo and dizziness in children. BPV: benign paroxysmal vertigo; CP: cerebellopontine; PPV: paroxysmal positional vertigo.

2.5 Discussion

2.5.1 Vestibular migraine

One of the most common diagnoses in children with vertigo and dizziness is migraine headache (i.e. migraine equivalent), although the temporal relationship has been reported to be variable[7]. In several clinical series, more than 50% of children experiencing dizziness also have headache[5,8] and migraine represents the most common primary headache in childhood; approximately 10% of children meet the International Headache Society (IHS) criteria for migraine headache[9].

The pathogenesis of vestibulopathy and its association with migraine are not known for certain. Pe´ rez-Plasencia et al.[10] have hypothesized that in the migraine patient, vertigo may be related to transitory vasospasm producing labyrinthine or central vestibular pathway ischemia. Cutrer and Baloh[11] suggested that vertigo could be caused by a unilateral, reversible neurochemical derangement in the vestibular periphery. Typical for VM are episodic attacks of rotatory vertigo lasting minutes to hours and followed or accompanied by headache and sensitivity to light and noise[12]. Interestingly, in children as in adults, vestibular symptoms of migraine may precede, accompany or follow the painful attacks: precritical, critical,

and postcritical vestibular manifestations, respectively[9]. Discrete central motor signs (saccadic pursuit) are commonly observed between attacks[12].

Marcelli et al.[9] reported vestibular findings in 22 children diagnosed with migraine. In this sample, 73% of the participants with migraine vertigo demonstrated either peripheral or central vestibular abnormalities. The vestibular manifestations varied and included spontaneous-positional nystagmus, post head-shaking nystagmus, BPPV, vibration-induced nystagmus, absence of vestibular evoked myogenic potentials (VEMPs), and unilateral or bilateral caloric reductions.

Establishing a diagnosis of VM has recently taken on additional importance as new treatments have become available. Identification and avoidance of environmental and dietary triggers, when possible, will reduce the need for pharmacotherapy. If conservative measures fail, the same medications used to prevent migraine (i.e. b-adrenergic blockers, calcium channel blockers, and tricyclic amines) are used to control vertigo spells[13].

When to use a pharmacologic preventive medication in a pediatric patient often depends on patient and caregiver preferences. It is generally reasonable to offer a daily preventive treatment when migraine attacks occur once a week, or whenever the attacks are particularly long or debilitating[14].

2.5.2 Benign paroxysmal vertigo

Benign paroxysmal vertigo (BPV) of childhood is defined as "a heterogeneous disorder that is characterized by recurrent brief episodic attacks of vertigo occurring without warning and resolving spontaneously in otherwise healthy children"[15]. It is considered a common cause of vertigo in children, occurring with a prevalence of 2.6%[5]. Onset of BPV has been reported to occur typically before 4 years of age and it is rarely seen after 8 years[7].

The physiopathology of this disorder is a matter of debate. Some authors have indicated an epidemiological link with migraine, leading the International Headache Society (IHS) to include this entity in its first International Classification of Headache Disorders under the chapter 'Childhood periodic syndromes that are commonly precursors of migraine'[16–18]. The pathogenesis of BPV is not yet known; dizziness seems to follow vascular alterations that produce a transient hypoxia of the vestibular nuclei and the vestibular pathways. The same phenomenon is involved in other brain districts throughout the classic migraine attack, according to the "vascular hypothesis"[15]. While the pathophysiology of BPV is currently unknown, there is

strong supporting evidence that BPV is a migraine headache variant as many children with BPV will go on to develop migraine later in life[7].

Concerning the clinical presentation, abnormal eye movements suggestive of nystagmus may be seen. There are no alterations of consciousness, neurological changes or signs of audiovestibular impairment during the entire attack[15]. In their study on 20 children with a diagnosis of BPV, Chang and Young[19] found abnormal responses in 7 (35%) patients at caloric test, and alterations of vestibular evoked myogenic potential (VEMP) in 10 (50%) patients. The combination of caloric test and VEMP results revealing a higher abnormality (70%) in BPV children appears to be a supplementary diagnostic tool for evaluating children with BPV. Moreover, several studies have reported that children with BPV commonly present with significant bithermal caloric asymmetry[20–22].

The prognosis of BPV is considered to be favorable by many authors as symptoms usually tend to disappear spontaneously before adolescence. Attacks may recur within a period of 6 months to 1 year and then disappear spontaneously without treatment[15]. Nevertheless, in their recent study on 17 patients, Krams et al.[23] found a persistence of attacks during adolescence in 50% of cases and a prevalence of migraine of 100% after age 15. On the basis of these findings, the concept of benignity usually associated with this disorder is called into question.

2.5.3 Head trauma

Head trauma in young children is common and dizziness/ vertigo is also a common symptom for a significant number of children presenting with trauma[7]. Blunt head injuries, including whiplash injuries, can lead to dizziness through fracture of the temporal bone or labyrinthine concussion[3]. In cases of a fracture or concussion where the labyrinth or vestibular nerve is affected, children can experience severe vertigo with nystagmus and nausea, indicating unilateral loss of function in the peripheral vestibular system (i.e. end-organ or vestibular nerve)[7]. Penetrating head injuries have been reported to cause vertigo secondary to perilymph fistula[24]. That occurrence should be suspected in cases of head trauma where the child presents with dizziness and/or hearing loss.

At present, there are only a few reports in the literature focusing on quantitative balance function testing in the diagnostic approach for trauma. Choung et al.[25] described test results in 55 pediatric patients with vertigo, four of whom were diagnosed with vertigo due to trauma. Although all four patients demonstrated normal

caloric examinations, they demonstrated abnormalities during rotational testing.

In one of the most comprehensive studies reporting the effects of blunt head injuries in children, Vartiainen et al.[26] described findings in 199 children. The investigators compared 61 children treated for acute blunt head injury with 59 age-matched controls. An additional 138 children with a previous diagnosis of blunt head trauma were invited for examination to determine post-traumatic findings in the long term. Of the 61 patients with acute head injury, only 1 (2%) complained of vertigo. Of 138 patients examined more than 12 months after head injury, two patients (1%) described vertigo. Surprisingly, reports describing findings on quantitative balance function testing in children post trauma are rare, with the exception of the large-scale study by Vartiainen et al.

Finally, one example of perilymph fistula was reported by Kojima et al.[27]. The investigators described vestibular manifestations in an 11-year-old boy who suffered a penetrating injury while rock-climbing. During the child's physical examination 2 weeks after injury, he demonstrated horizontal nystagmus, hearing loss, and significant positional nystagmus. The presence of perilymph fistula was confirmed during exploratory surgery.

2.5.4 Vestibular neuritis

While the cause of vestibular neuritis is somewhat controversial, many investigators have suggested that it is viral in origin, though bacterial and other types of infections have also been suggested[28].

In their study on 17 children affected by vestibular neuritis, Tahara et al. [29] found an upper respiratory tract infection preceding the symptoms in 53% of all cases. Similarly, in 21 children studied, Taborelli et al.[30] observed a rate of 47% for upper respiratory tract infection before the onset of vestibular neuritis.

Children suffering from an attack of vestibular neuritis often present with the same symptoms as their adult counterparts[2,5]. Concerning positional and positioning nystagmus in the child, this has generally been observed in the early disease phase (at about 15 days from onset)[30].

However, in their study on long-term follow-up after vestibular neuritis, Taborelli et al.[30]noted this type of nystagmus, beating on the healthy side, still present in about 5% of the children after 2 years. The authors found a complete disappearance of symptoms after 1 year apart from five patients, whereas a unilateral canal paresis was still present after 2 years in 14% of the cases. Among balance func-

tion tests, the caloric examination is the gold standard for documenting the side and degree of peripheral vestibular impairment, and can provide information with regard to the integrity of the lateral semicircular canals and/or superior vestibular nerves[7].

Rotational testing can also be a useful tool in assessing children with suspected vestibular neuritis. Choung et al.[25] reported the results of positional, rotational, and caloric testing in 55 children with the chief complaint of vertigo or dizziness, one of whom was diagnosed with vestibular neuritis. This patient demonstrated unilateral caloric weakness and no significant positional nystagmus. In addition, abnormal gain, phase, or symmetry (not specified by the investigators) of the vestibulo-ocular reflex (VOR) was observed during rotational testing, with normal VOR fixation, further suggesting a peripheral origin of the dizziness.

In a review of 282 children with vertigo by D'Agostino et al.[31], two children diagnosed with vestibular neuritis demonstrated spontaneous nystagmus and positive Romberg sign, and one demonstrated "moderate" positional nystagmus.

In general, there is a paucity of data describing the effects of central nervous system compensation in children and how this can affect quantitative vestibular testing. While these data are available in adults, it is currently unknown how the rate of recovery is different in children with vestibular neuritis.

2.5.5 Middle ear effusion and otitis media

Vertigo and dizziness in childhood are often caused by otitis media (OM) and middle ear effusion (MEE), which represent two of the most common diseases in children[32]. Because most children with abnormal middle ear ventilation do not report balance disturbance or vertigo, the symptoms are usually reported by their parents who describe clumsiness, awkwardness, and sometimes, frequent falling.

Different theories have been proposed as to how middle ear pathologies can affect the vestibular labyrinth. Golz et al.[32] postulated that toxins present in middle ear fluid enter the inner ear fluid and cause serous labyrinthitis. Other researchers have proposed that pressure changes in the middle ear cause displacements of the round and oval windows, leading to secondary movement of labyrinthine fluids[33].

Golz et al.[32] used electronystagmographic (ENG) recordings to compare 136 children with a history of MEE and 74 children without a history of MEE. Neither study group showed abnormalities during optokinetic or pursuit testing. However, 42 children with MEE (31%) demonstrated spontaneous nystagmus, and 24 (17.5%)

showed positional nystagmus consistent with BPPV. Thirteen children showed both spontaneous and positional nystagmus. Therefore, 79 children with MEE (58%) had abnormal ENG findings compared with three children (4%) in the control group. In 77 children, a second evaluation was performed after ventilation tube placement and only three children (4%) still showed abnormal electronystagmographic recordings.

In line with this study, Koyuncu et al.[34] evaluated spontaneous and positional nystagmus in 30 children with MEE and 15 matched controls. Spontaneous nystagmus of greater than 78/s was observed in 1 child with MEE, and positional nystagmus was observed in 10 children with MEE. The control group demonstrated no abnormalities on ENG testing. The study group was then reevaluated 1 month following myringotomy and tube insertion. No spontaneous or positional nystagmus was observed postoperatively.

Casselbrant et al.[35] reported a higher velocity of sway in a group of 41 children with OM compared to children with no ear disease. Similarly, in their study on 34 patients, Jones et al.[36] found that body sway was more pronounced in children with OM compared with a control group. Moreover, the authors reported the elimination of those differences by treatment of OM by myringotomy and insertion of ventilation tubes.

2.5.6 Me´nie‘re’s disease

Me´ nie‘ re’s disease (MD) is characterized by idiopathic attacks of vertigo and auditory symptoms. According to the American Academy of Otolaryngology, the diagnosis of definite MD requires at least two attacks of vertigo lasting more than 20 min and tinnitus and/or fullness in the affected ear, as well as documented hearing loss on at least one occasion[37].

The symptoms of MD usually start in middle age, especially between 30 and 50 years of age, and MD is probably quite rare in children. Nevertheless, this pathology may represent a possible cause of vertigo in the pediatric population.

The incidence of MD in pediatric patients with vertigo or equilibrium disturbance was reported as 1.5% by Hausler et al. [38], 3.1% by Fujii et al. [39] and 4% by Bower et al.[2]. In their analysis on 103 young patients with vertigo, Akagi et al.[40] found an incidence of MD of 2.9%.

In general, the majority of reported children are 10 years and older but a recent report by Miyahara et al.[41] showed a 5-yearold girl with symptoms and auditory

findings indicating definite MD. This study emphasized that a young child may not describe hearing symptoms such as tinnitus and/or fullness, which is a requirement for the diagnosis of definite MD.

In agreement with Miyahara's observations, Brantberg et al.[42] described four children in whom symptoms suggesting MD started at 4–7 years age. However, in all four patients, an occasional sensation of fullness or tinnitus in the affected ear was only reported in subsequent years.

Concerning therapy options, based on the similarity in clinical features between migraine and MD, Sørensen[43] used dihydroergotamine and reported the effectiveness of the drug in pediatric patients with Me´ nie' re's disease. Filipo and Barbara[44] suggested that diuretics should be used as the first-choice drug, while Meyerhoff et al.[45] reported the usefulness of endolymphatic sac drainage surgery in pediatric patients with Me´ nie' re's disease.

2.6 Conclusion

Vertigo and dizziness are not particularly rare occurrences in children. If present, both these symptoms seriously interfere with the intellectual and physical development of the child although they can be missed for a long time owing to the failure of many children to communicate clearly. Therefore, the role of the physician becomes fundamental to aid in rapid diagnosis and instigate appropriate treatments when a vestibular pathology is suspected. In particular, when approaching this topic, the otolaryngologist should always consider all of the possible entities connected with these symptoms, even those typically managed by other specialists.

Overall from our review, it can be noted that, in comparison to other pathological entities, VM and BPV are more frequently connected with episodes of vertigo in young patients. Nevertheless, the sparse number of studies investigating this topic and their different modalities in patient cohort selection concur to hide the real incidence of different vestibular disorders in children. In this sense, the choice of some authors to exclude patients suffering from otitis media or middle ear effusion from their studies appears unhelpful. Moreover, the absence of a well standardized diagnostic protocol for children's vestibular examination represents another important drawback.

For these reasons, new randomized controlled trials on larger cohorts of patients should be organized with the aim of defining the real incidence of every vestibular

disorder in childhood and to better describe their clinical characteristics.

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Chapter 3

Title: Clinical features of colorectal cancer patients in advanced age: a population-based approach

Authors: Stefania Maffei, Alessandra Colantoni, Shaniko Kaleci, Piero Benatti, Ester Tesini, Maurizio Ponz de Leon.

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3.1 Abstract

In the immediate future, the number of geriatric patients will continue to rise; consequently we should expect an increase of colorectal cancer, a disease of the elderly population. Through the data of a Cancer Registry, we examined (a) the effect of ageing on the main features of colorectal cancer; (b) changes in management, especially for individuals older than 80 years; and (c) changes in prognosis and survival in subgroups of patients with different age. The Registry provided information on colorectal cancer up to 2010 (27 years). A total of 5293 patients were registered; these were divided into three groups: A (0–64 years), B (65–79) and C (80 or more). Three periods of observation were chosen: 1 (1984–1992), 2 (1993–2001) and 3 (2001–2010). Group A included 1571 patients (29 %), Group B 2539 (48 %) and Group C 1183 (22.3 %). The fraction of old individuals increased during the 27 years of the investigation. In these patients, tumours were predominantly localized to the right colon (42.6 %). The rate of surgery and ratio between curative and palliative approaches were similar among the three groups ($p<0.38$). There

was disparity ($p<0.002$) in the administration of chemotherapy (5.8 % of the elderly vs 34.4 % in remaining patients). Survival increased over time in all three groups. In the elderly, average 5-year survival was 31 % in period 1 and 55 % in period 3. These data show that in Western countries, the standard of care for colorectal cancer diagnosed in geriatric patients has improved over the last 30 years.

3.2 Introduction

Despite advancements in molecular biology, early detection and treatment, colorectal cancer remains one of the most frequent causes of morbidity and mortality for neoplasms in the Western World, including Italy[1,2]. Moreover, there are several suggestions that the disease is also increasing in frequency in many developing countries[3].

Several factors have been identified, which are associated with the risk of large bowel tumours, in particular, inheritance, diet, life style, and the progressive increase of the elderly population[4–7]. As a matter of fact, data from many cancer registries indicate that at least in Western countries, more than 50 % of these patients are above the age of 70 years[8].

If we consider that during the immediate future, the number of elderly people will continue to increase, we would expect a further increase in the incidence of colorectal cancer, especially in individuals older than 70 or 80 years. The rising burden of these patients strongly suggests a need to investigate in more detail the possible effect of ageing on the most relevant epidemiological, clinical and pathological features of colorectal cancer.

Through the data of a population-based, specialized Colorectal Cancer Registry, instituted in 1984 in the Health Care District of Modena (Northern Italy), the main objectives of the present study were (a) to evaluate the effect of age and ageing on the pathological and clinical features of patients with a diagnosis of colorectal malignancy; (b) to ascertain changes in the management of colorectal cancer patients—during the period 1984–2010— with particular attention to individuals older than 80 years; and (c) To assess changes in prognosis and survival in subgroups of patients of different ages.

3.3 Materials and methods

3.3.1 The registry

Details on the specialized colorectal cancer Registry have been given in several previous reports[9,10]. Briefly, the District includes Modena and 10 smaller communities, for a total of 278,511 residents (137,052 males, and 141,459 females) at census 2001. Modena is located in Northern Italy, nearby in the centre of Padana flat, 180 km south-east of Milan. The area is highly industrialized, almost exclusively urban, and with one of the highest levels of income per person in Italy. The age structure of the resident population is typical of well-developed and industrialized countries, with small numbers of infants and young individuals, and a progressively increasing elderly population, more marked in women. From January 1984 to December 2010, 5293 patients affected by colorectal malignancies were recorded in the Registry. Crude incidence rate tended to increase gradually during the registration period, in the range of 50–95 new cases/100.000 inhabitants/year.

3.3.2 Study groups

Registered patients were divided into three groups according to their age: Group A (0–64 years), Group B (65–79 years) and Group C (80 years or older). Clinical records were used to gather information on gender, age at diagnosis, tumour site (and subsite), histological features, pathology stage, surgical approach, chemotherapy and other relevant clinical characteristics. As far as sublocalization in the large bowel was concerned, we consider the colon–rectum as divided into three anatomical subsites: right colon (Appendix, Caecum, Ascending, Hepatic Flexure, Transverse and Splenic Flexure), Left colon (Descending and Sigmoid) and Rectum (Rectosigmoid junction, Rectum and Anus). The subdivision reflects differences in biology and epidemiologic features of commonly occurring colorectal malignancies[11–13].

Neoplasms were classified and staged according to the International Classification of Diseases (Tenth Edition)[14]. TNM Stage of tumours was evaluated in 4995 patients out of 5293 (i.e., those with histological features of epithelial and glandular neoplasms); we did not stage 36 patients with carcinoid tumours, 20 with colorectal lymphoma, 49 with squamous cell carcinoma, 13 with gastrointestinal stromal tumours (GIST), 11 with Kaposi sarcoma and 177 patients with preoperative radiotherapy, usually staged with the Dworak regression index[15].

In order to investigate changes in colorectal cancer features, treatment and clinical outcome in older patients (versus other groups) over time, we arbitrarily subdivided the registration into three periods: 1984–1992 (period 1), 1993–2001 (period 2) and 2002–2010 (period 3).

3.3.3 Statistical analysis

Analysis of data was usually carried out with patients stratified by age. Chi-square or Fisher's exact tests were executed in order to evaluate age-related differences in clinical and pathological features, as well as treatment options. Disease-specific survival (DSS) and Overall (OS) survival were assessed with the Kaplan–Meier method; the statistical significance in survival differences among groups, in the three periods of registration, was evaluated with Log-Rank test [16]. Poisson regression analysis was applied to analyse trends of colorectal cancer incidence throughout the registration period. Data were computed using the Statistical Package for Social Sciences software (IBM SPSS Statistic 2010) and the Statistical software STATA 13 (College Station, TX, Stata Corp. L.P.). Statistical significance was set at $p<0.05$.

3.4 Results

The main clinical features of registered patients, stratified into three groups, are illustrated in Table 3.1. Group A included 1571 patients (29 %), of these 884 were men, and 687 women; Group B included 2539 individuals (48 %), 1463 men, and 1076 women; Group C (the elderly population, $\geq$80 year old) included 1183 patients (22.3 %), 543 were men and 640 women. As it is clearly shown, there were more women among elderly patients, and the difference is highly significant. This is of interest, since tumours of the large bowel tend to be more prevalent in the male gender [17], at least in Western countries.

The fraction of patients older than 80 increased progressively throughout the registration period (from 17.4 to 49.3 %), that is, nearly one half of the elderly were observed in the 9-year period 2002–2010; $p<0.001$). As far as sublocalization of tumours in the large bowel was concerned, tumours tended to predominate in the left colon and rectum in Group A and B patients; in contrast, in elderly patients, almost half of the lesions (42.6 %, 504 of 1183) were localized in the right colon ($p<0.001$). Stage was more difficult to interpret; in all three groups, the majority of

tumours were staged TNM II or III. However, there was a clear tendency either for early (I) or for advanced (IV) lesions to be less prevalent among elderly individuals. Patients were classified by the number of lymph nodes harvested in the resected sample (0, 1–11, 12+); no apparent difference was observed among the three groups of patients concerning the number of examined lymph nodes. Rather unexpectedly, we did not observe any consistent or significant difference, among the three groups of patients, in the general rate of surgery, and in the ratio between curative and palliative approaches. In other words, elderly individuals were operated to the same extent, and with the same modalities as other patients of younger age ($p<0.56$). In contrast, we observed a highly significant ($p<0.001$) disparity in the administration of chemotherapy with increasing age of patients: only 5.8 % (58 of 1183) of elderly patients (Group C) received chemotherapy, versus an average 34.3 % in the two other groups.

Variables	Total ($n = 5293$)	Group A ($n = 1571$) 0–64 years (29.7 %)	Group B ($n = 2539$) 65–79 years (48.0 %)	Group C ($n = 1183$) 80+ years (22.3 %)	p value
Sex					
M	2403 (45.4 %)	884 (56.3)	1463 (57.6)	543 (45.9)	**<0.001**
F	2890 (54.6 %)	687 (43.7)	1076 (42.4)	640 (54.1)	
Years of diagnosis					
1984–1992	1292 (24.4 %)	457 (29.1)	629 (24.8)	206 (17.4)	**<0.001**
1993–2001	1805 (34.1 %)	509 (32.4)	902 (35.5)	394 (33.3)	
2002–2010	2196 (41.5 %)	605 (38.5)	1008 (39.7)	583 (49.3)	
Tumour location					
Right	1846 (34.9 %)	463 (29.5)	879 (34.6)	504 (42.6)	**<0.001**
Left	1883 (35.63 %)	608 (38.7)	906 (35.7)	369 (31.2)	
Rectum	1556 (29.4 %)	496 (31.6)	752 (29.6)	308 (26.0)	
Nn	8 (0.2 %)	4 (0.3)	2 (0.1)	2 (0.2)	
Stage (TNM)[#]					
I	868 (17.4 %)	265 (18.4)	455 (18.9)	148 (12.9)	**<0.001**
II	1529 (30.6 %)	429 (29.8)	738 (30.6)	362 (31.6)	
III	1199 (24.0 %)	343 (23.8)	572 (23.7)	284 (24.8)	
IV	1027 (20.6 %)	347 (24.1)	486 (20.2)	194 (16.9)	
Nx*	104 (2.1 %)	26 (1.8)	58 (2.4)	20 (1.7)	
Ns[§]	268 (5.4 %)	30 (2.1)	101 (4.2)	137 (12.0)	
Surgery					
Curative	4415 (87.6 %)	1342 (88.5)	2133 (87.0)	940 (87.5)	0.380
Palliative	626 (12.4 %)	174 (11.5)	318 (13.0)	134 (12.5)	
Number of lymph nodes					
0	191 (4.7 %)	51 (4.2)	91 (4.6)	49 (5.4)	0.566
1–11	1617 (39.6 %)	486 (40.2)	787 (40.1)	344 (37.6)	
12+	2276 (55.7 %)	671 (55.5)	1084 (55.2)	521 (57.0)	
Chemoterapy					
No	2688 (65.1 %)	523 (44.5)	1231 (63.0)	934 (93.7)	**<0.001**
Yes	1416 (34.3 %)	647 (55.1)	711 (36.4)	58 (5.8)	
Na°	23 (0.6 %)	5 (0.4)	12 (0.6)	5 (0.5)	

Bold values indicate statistically significant p values ($p < 0.001$)

SD standard deviation

[#] We excluded patient affected only by carcinoid (11), lymphoma (13), squamous cell carcinoma (24), GIST (10) and patient treated with radiotherapy: dworak 0 (22), dworak1 (35), dworak 2 (22), dworak 3 (9), dworak 4 (17)

* *Nx* tumours with no lymph nodes collected during surgery [§] *Ns* tumours with insufficient histopathological and clinical documentation for staging

° Na information not available

Table 3.1: Main clinical and pathological features of colorectal cancer patients stratified into three age groups

The trend of incidence of colorectal cancer—according to age, tumour location, gender and stage—was examined by Poisson regression analysis (Table 3.2). IRR (Incidence Rate Ratio) rose sharply throughout the registration period in Group C, thus indicating that while the number of relatively young individuals showed little variation, the absolute number of elderly individuals increased significantly over time (from 1.0, reference category, to 2.77). The analysis confirmed a predominance of colorectal cancer in the female gender among subjects of advanced age; moreover, though tumour localization in the large bowel did not change appreciably over time, elderly patients were diagnosed more often with right-sided tumours as compared to younger individuals. IRR for stage was more difficult to evaluate; however, the analysis did not show marked differences in the three study Groups, and confirmed the predominance of tumour in the two intermediate classes (II and

III, corresponding to Dukes' B and C).

Variables	Group A (0–64 years)		Group B (65–79 years)		Group C (80+ years)	
	IRR	95 % IC	IRR	95 % IC	IRR	95 % IC
Period of registration						
1984–1992	1.00		1.00		1.00	
1993–2001	1.06	0.93–1.21	**1.42**	**1.28–1.57**	**1.94**	**1.63–2.30**
2002–2010	**1.28**	**1.13–1.46**	**1.57**	**1.42–1.74**	**2.77**	**2.36–3.26**
Gender						
Female	1.00		1.00		1.00	
Male	**1.285**	**1.16–1.43**	1.02	0.94–1.10	**0.40**	**0.36–0.45**
CRC location						
Right colon	1.00		1.00		1.00	
Left colon	**1.35**	**1.19–1.52**	1.03	0.94–1.13	**0.74**	**0.65–0.85**
Rectum	0.88	0.76–1.00	**0.72**	**0.65–0.80**	**0.56**	**0.48–0.65**
Stage						
TNM I	1.00		1.00		1.00	
TNM II	**1.61**	**1.38–1.88**	**1.62**	**1.44–1.82**	**2.44**	**2.02–2.96**
TNM III	**1.29**	**1.10–1.51**	**1.25**	**1.11–1.42**	**1.91**	**1.57–2.34**
TNM IV	**1.30**	**1.11–1.53**	**1.07**	**0.94–1.21**	**1.31**	**1.05–1.62**

IRR incidence rate ratio
In bold $p \leq 0.05$

Table 3.2: Results of the Poisson regression analysis: period of registration (reference category: 1984–1992), Gender (reference: female), CRC location (reference: right Colon), stage (reference category: TNM I)

Kaplan–Meier statistics was used to evaluate 5-year survival—either disease-specific survival (DSS) or overall survival (OS)– in the three groups of patients and during the three registration periods (1984–1992; 1993–2001; 2002–2010). Patients were censored at their last follow-up, as being alive or deceased; in this case, the cause of death was recorded. As shown in Fig. 3.1, DSS increased significantly over time, and to the same extent, in all three groups of patients. In the elderly population, in particular (Group C), survival increased from 31 % in period 1 (1984–1992) to 55 % in period 3 ($p<0.01$). A similar trend was observed for OS in Group 1 and 2; as expected, overall survival showed only minor variations in elderly individuals, with a modest insignificant benefit for elderly patients registered in the most recent years.

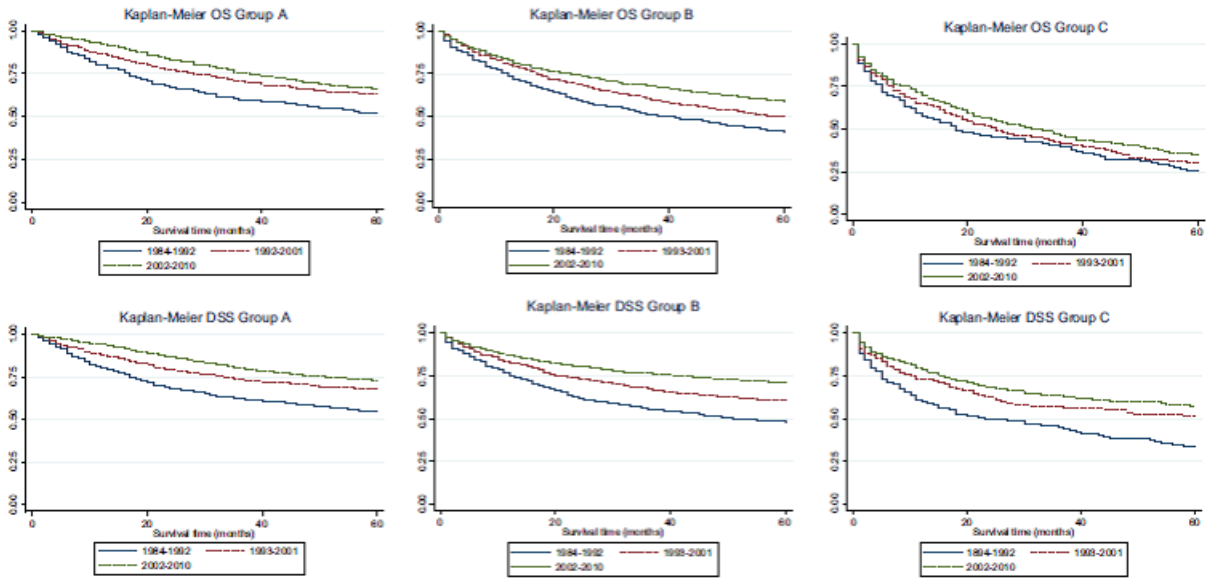

Figure 3.1: 5 year, disease-specific survival (DSS) and overall survival (OS) by period of registration

3.5 Discussion

The results of the present study can be summarized as follows. First, some 22 % of all patients with colorectal malignancies are diagnosed over the age of 80 years, and this fraction will presumably increase in the future. Second, while colorectal tumours are more prevalent in the male gender (in most Western countries), in the elderly, these neoplasms seem to be more frequent in the female gender. Third, in older people, colorectal tumours tend to localize in the proximal large bowel, from the ceacum to the splenic flexure, and the event seems more frequent in most recent years of observation. Fourth, disease-specific survival increased significantly over time in all the investigated groups of patients, independently of age. Fifth, the fraction of elderly individuals who underwent surgery was similar to that of individuals of younger age; moreover, palliative surgery was executed in some 12.0 % of all patients, irregardless of age. Finally, a highly significant disparity was noted in the administration of chemotherapy with increasing age of patients, as only 6 % of patients over 80 years were treated as opposed to almost 35 % in the other groups.

With the increase of age of the general population, in the near future, the num-

ber of elderly individuals who will present with colorectal malignancies is going to increase. However, since old patients are usually not included in trials and in most clinical investigations, there is still limited information about the age-related changes of colorectal cancer characteristics. Thus, it is important—especially for social and economic reasons—to focus on features, standard of care and outcome of colorectal carcinoma that develops in elderly individuals.

Frequently in treating old patients, the demographic age is the only variable taken into consideration, while little attention is paid to the biological and clinical age. The socalled "ageism" may lead to the provision to the elderly of a poor standard of care, so that they are frequently undertreated. In contrast, a correct attitude towards old patients implies an accurate clinical evaluation that takes into consideration their specific physiological and pathological conditions[18].

We examined cancer characteristics, pattern of treatment and outcome during a 27-year period, taking advantage of a specialized colorectal cancer Registry[9,10]. Patients were divided in three age groups according to their age at registration, so that three 9-year intervals (1984–1992, 1993–2001 and 2002–2010) could be studied. As already reported, a consistent increase over time in the number of colorectal malignancies was observed[11]. However, the most impressive result of the present investigation is the marked increase in the incidence of colorectal cancer observed over time in patients aged more than 80 years. These findings can be due to several reasons, some of which are probably obscure; we believe that one of the contributing factors is the high number of endoscopic procedures carried out on the elderly population as part of cancer screening. As a matter of fact, many individuals in their eighties continue colorectal cancer screening throughout their lives[19]. Moreover, this could be one of the reasons of the increased survival rate observed in the elderly (Fig. 3.1), with a consequent healthier ageing of the population.

Our data confirm the age-related migration of colorectal cancer localization from left to right colon[19–21]. Again, besides possible biological explanations, this migration can be attributed to the widespread diffusion of endoscopic techniques.

The choice of surgical approach in individuals with colorectal cancer at the age of 80 years or more has provided contrasting results. Thus, Gun Min Kim et al. report that more than 95 % of elderly patients, in their experience, undergo surgical treatment; moreover, Mastracci et al. suggest that patients older than 80 years who are selected for surgery have a quality of life comparable to that of younger patients[22,23]. On the other hand, Aparicio et al. report that only 60 % of elderly people with colorectal cancer are usually treated, while Kunitake et al. point out

the high rates of morbidity, mortality and readmission to hospital of octogenarian patients with colorectal cancer who undergo main surgery of the large bowel[24,25] . The reasons for such discrepancies remain unclear, but may depend, at least in our opinion, on many factors, including selection of patients, different occurrence of comorbidities and the individual experience of surgeons.

In the present study, some 90 % of patients underwent surgery despite older age. Moreover, the rate of treatment rose from 78 % in period 1 (1984–1992) to 89.3 % in period 3 (2002–2010), an increase that can be attributed to a general improvement in management of colorectal cancer patients, as it is also shown by the increasing (over time) number of harvested lymph nodes in the resected colorectal specimens[26]. Presumably, advances in surgical techniques, anaesthetic procedures and post-operative care rendered surgery less hazardous for old individuals. We do believe that the outcome for elderly patients who undergo colorectal surgery is probably similar—at least in many instances—to that of younger patients. This is probably due to a more careful selection of patients, and to an increased attention to performance status and comorbidities[27].

We were rather surprised that only 5.9 % of patients in their eighties (Group 3) received chemotherapy. This treatment is given to eradicate micrometastasis (adjuvant) or to prolong survival in patients who cannot be operated (palliative). We found very little information on the use of chemotherapy in elderly individuals with colorectal malignancies, either as an adjuvant or palliative approach. The use of cytotoxic drugs in this clinical setting remains controversial, owing to toxicity and side effects[28]. Esteva et al. report similar findings[29]. The Authors report less use of chemotherapy and of radiotherapy in elderly patients with colorectal neoplasms, and attribute this to several reasons, including concerns about toxicity, role of comorbidities and a negative impact on quality of life.

3.6 Conclusions

This is a population-based (i.e., through a Registry) analysis that reports colorectal cancer characteristics, treatment and clinical outcome in geriatric patients over the age of 80 years, taking into account an observational period of 27 years. On the basis of our data, it seems that in the Western World, the standard of care for colorectal cancer in geriatric patients has significantly improved. Compliance with ethical standards Conflict of interest The authors declare that they have no con-

flict of interest. Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with human and animals performed by any of the authors.

Informed consent None.

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Chapter 4

Title: Disease presentation, treatment and survival for Italian colorectal cancer patients: a EUROCARE high resolution study

Authors: Pamela Minicozzi, Shaniko Kaleci, Stefania Maffei, Claudia Allemani, Adriano Giacomin, Adele Caldarella, Francesco Iachetta, Mario , Rosario Tumino, Massimo Vicentini, Fabio Falcini, Rosaria Cesaraccio, Maurizio Ponz de Leon, Milena Sant.

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4.1 Abstract

We analysed presentation, treatment and survival in a representative population-based sample of 3753 Italian colorectal cancer cases, diagnosed 2003–05: 70% were >65 years, 44% stage I-II, 27% stage IV and 92% received surgery. Chemotherapy was given to 58% of stage III colon cases, radiotherapy to 25% of rectal cases. Four percent of surgical cases underwent endoscopic polypectomy, and in 57% 11 lymph nodes were examined. Five-year relative survival was good (60%), independent of sex and site. Adherence to treatment guidelines was satisfactory, but wider use of faecal blood testing and colonoscopy will anticipate stage at diagnosis and likely improve survival.

4.2 Introduction

Colorectal cancer is one of the commonest cancers in Europe, with higher incidence in Western than Central and Southern Europe. Although internationally agreed guidelines for diagnosis and treatment are available, and screening can effectively identify earlystage lesions, survival varies markedly across Europe. Thus, 5-year relative survival (RS) for European colorectal patients alive at some point in 000–02 ranged from 30% to 65% (60% overall)[1].1 Such variation might be owing to differences in stage at diagnosis or variable adherence to treatment guidelines[2].

The present EUROCARE-5 high-resolution (HR) study provides an overview of colorectal cancer presentation, treatment and survival for Italian patients diagnosed in 2003–05. The overview was obtained by analysis of a representative population-based sample of cases archived in eight Italian cancer registries (CRs), with detailed information on stage at diagnosis, treatment, etc., obtained by consultation of clinical records.

4.3 Methods

In conformity with the Italian EUROCARE-5 HR protocol, 500 primary colorectal cancers diagnosed in 2003–05 were selected for each of the participating CRs (Biella, Modena, Romagna, Reggio Emilia, Firenze, Napoli, Ragusa and Sassari) by a random procedure balanced for year of diagnosis, from cases archived in the Italian Association of Cancer Registries database. International Classification of Diseases, 3rd revision, codes identified right colon (C18.0–C18.5), left colon (C18.6–C18.7), unspecified colon (C18.8–C18.9) and rectal (C19.9–C21.3) sites. After excluding cases with unspecified colon subsite, 3753 cases were analysed. Cases were followed-up to the end of 2008, except for Firenze and Ragusa, for which life status information was, respectively, completely or partially (50%) updated up to the end of 2007.

Age at diagnosis (15–54, 55–64, 65–74, 75–99 years); TNM stage (I, II, III, IV, unknown), chemotherapy, radiotherapy and surgery (done, not done, unknown); type of surgery [hemi-colectomy, Miles' operation, segmental resection (= any other kind of resection), endoscopic polypectomy, palliative surgery (= any kind of surgery leaving residual tumour), unknown]; number of total harvested lymph nodes (1–10, 11, unknown); and recurrences in the 5 years following diagnosis (none, local/regional, distant metastases, unknown recurrence or type of recurrence) were obtained by directly accessing clinical/pathological records.

Overall and for each subsite, the distribution of above variables was analysed. Differences in proportions, tested by the two-sided z test, were considered significant for P<0.05. Five-year RS (Ederer II method[3]) was age-standardized (where pertinent) by the direct method using the International Cancer Survival Standards age distribution[4]. Differences in age-standardized survival were investigated by generalized linear models assuming a Poisson distribution of deaths[3].

Analysis of lymph nodes harvested was restricted to 3326 cases undergoing non-polypectomy surgery. Analysis of recurrence was restricted to 2055 cases (excluding stage IV cases, and cases from Firenze and Reggio Emilia for lack of recurrence information for 93% and 28% of cases, respectively). Survival analysis was restricted to 2823 cases (excluding Firenze and Ragusa cases for lack of updated life status, and 16 other cases known by death certificate only or discovered at autopsy). The Stata statistical package was used.

4.4 Results

Overall, 11% of 2533 colon and 1220 rectal cases were 15–54 years at diagnosis, and 70% were >65 years. About 40% of cases were stage I or II; 27% were stage IV. Stage I plus II, and stage III plus IV proportions were similar in colon and rectal cases (P > 0.05).

For surgical cases (1231 right colon, 1158 left colon, 1078 rectum), hemi-colectomy was performed in >80% of right colon and 51% of left colon cases; segmental resection was performed in >60% of rectal and 33% of left colon cases. Miles' operation was limited to 13% of rectal cases, and endoscopic polypectomy to 4% of cases (with no sub-site variation). For the 57% of cases undergoing non-polypectomy surgery, 11 lymph nodes were examined: proportions were higher for right (69%) than left colon (61%) and rectal (49%) cancers. Lymph node information was lacking in 14% of cases, range 10 (right colon) to 18% (rectum).

Overall, 1456 cases received chemotherapy, with small differences between subsites, but marked differences according to stage [8% of stage I to 59% of stage III (58% colon, 61% rectum)] and age (78% of stage III cases <75 years, 25% for those 75 years). Only 332 cases (302 rectal) received radiotherapy, corresponding to 25% of rectal and 1% of colon cases.

Recurrences within 5 years were more common for rectal than colon cancers (30% vs. 24%, P = 0.03), and were fairly low (9%) for stage I disease, increasing

to 25% for stage II and 38% for stage III. Distant metastases were more common than local/regional recurrences for both colon (13% vs. 5%) and rectal (16% vs. 7%) cancers ($P < 0.05$). Age-standardized 5-year RS (table 1) was about 60% overall, for both sexes, with no differences between colon and rectal sites. RS decreased with advancing age and stage.

4.5 Discussion

This HR investigation provides an overview of the presentation, treatment and survival of Italian colorectal cancer cases diagnosed in 2003–05. A major finding is that, for both sexes and both sites, 5-year RS was around 60%, in line with estimates for European cases as a whole[1]. Survival was strongly influenced by stage, which remains the most important outcome predictor for these cancers. Notwithstanding increased use of faecal occult blood screening and colonoscopy in Italy[5], 27% of cases were stage IV at diagnosis.

Right or left hemi-colectomy, accompanied by complete removal of associated lymph nodes, was the main treatment for colon cancer, which is considered standard of care[6]; the disabling Miles' operation was seldom used. Endoscopic polypectomy was not widely used although it is considered the preferred approach for adenomatous and some malignant polyps[7].

The high proportion of cases with 11 lymph nodes harvested is evidence of generally good surgical practice. Although 14% of cases had missing node information, about 60% of these were 75 years, and often received palliative surgery only, or neo-adjuvant radiotherapy—which renders nodes difficult to identify.

Fifty-eight percent of stage III colon cases were given chemotherapy, in line with 62% reported for Dutch colon cases[8], but low compared with the 69% reported for French cases[9]. Strangely, 8% of all cases received chemotherapy for stage I disease although no data support this policy. Perhaps markers of tumour aggressiveness—not available in this study—guided this choice. By contrast only 25% of rectal cancers received radiotherapy compared with 60% in a similar Dutch population[10]. Nevertheless, 90% of all cases given radiotherapy had rectal cancer in line with ESMO guidelines. Of the remaining colon cases, 33% involved the sigmoid colon and 30% were stage IV, providing some rationale for radiotherapy use.

As expected, recurrences were more frequent for rectal than colon cases, and for stage III than earlier stage cases. However stage I and II cases had non-negligible

recurrence rates, suggesting that molecular markers should be investigated to predict aggressive behaviour in early-stage disease and select cases for adjuvant therapy (targeted or otherwise)[11].

	Colon			Rectum			All		
	N cases	RS (%)	95% CI	*N* cases	RS (%)	95% CI	*N* cases	RS (%)	95% CI
Not age-standardized estimates									
Total cases	1935	58.8	55.9–61.7	888	55.5	51.2–59.6	2823	57.8	55.4–60.1
Age at diagnosis (years)									
15–54	199	65.6	57.7–72.5	112	66.0	54.8–75.2	311	65.6	59.2–71.3
55–64	392	68.5	63.2–73.3	175	60.0	50.8–68.2	567	65.9	61.3–70.1
65–74	599	61.3	56.2–66.1	287	59.3	52.1–66.1	886	60.6	56.5–64.6
75–99	745	49.3	43.7–54.9	314	45.7	37.6–53.9	1059	48.3	43.7–52.9
Age-standardized estimates									
Total cases	1935	60.4	57.4–63.2	888	56.9	52.6–60.9	2823	59.2	56.8–61.5
Sex									
Male	1046	60.7	56.6–64.6	527	56.0	50.2–61.4	1573	59.0	55.6–62.2
Female	889	59.4	55.0–63.5	361	58.3	51.8–64.2	1250	59.1	55.7–62.6
TNM stage									
I	296	94.5	85.5–98.0	167	96.4	83.4–99.2	463	96.4	88.9–98.9
II	587	87.8	82.8–91.5	220	76.3	67.1–83.2	807	84.6	80.4–88.0
III	489	61.3	55.7–66.4	227	53.5	44.8–61.4	716	57.9	53.0–62.5
IV	537	13.6	10.4–17.3	232	11.3	7.1–16.5	769	10.6	7.9–13.8
Unknown	26	60.1[b]	29.9–87.0	42	60.9	35.0–79.1	68	66.6	46.8–80.5

[a]Cases from 6 of the 8 participating cancer registries after excluding those known by death certificate and incidentally discovered at autopsy. See text for details.
[b]Not age-standardized relative survival reported because of missing age-specific survival estimates.

Table 4.1: Estimates of 5-year relative survival (RS), with 95% confidence intervals (CI), for 2823a colorectal cancer cases, by age, sex and stage

To conclude, although 5-year survival was relatively high and adherenceto treatment guidelines satisfactory, survival can probably be further improved by increased use of faecal occult blood testing, colonoscopy and endoscopic polypectomy to reduce the proportion of cases diagnosed at advanced stage.

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Chapter 5

Preoperative Predictors of Successful Surgical Treatment in the Management of Parapneumonic Empyema

Authors: Alessandro Stefani, MD, Beatrice Aramini, MD, Giovanni della Casa, MD, Guido Ligabue, MD, Shaniko Kaleci, PhD, Christian Casali, MD, and Uliano Morandi, MD

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5.1 Abstract

Background: Video-assisted thoracoscopic surgery (VATS) and thoracotomy are the main surgical options for treating parapneumonic empyema. The choice of either operation depends on many preoperative features, including the patient's condition, clinical and radiologic findings, and pleural fluid characteristics. The identification of the combination of those preoperative findings that will allow surgeons to select the appropriate approach for a successful operation (VATS or thoracotomy) could be of great interest in clinical settings. Methods. We retrospectively reviewed a series of 97 patients who had undergone successful VATS or thoracotomy for parapneumonic empyema; in all cases, the operation had begun through VATS and was changed to a thoracotomy if a complete decortication was needed. Preoperative clinical, radiologic, and laboratory features were compared between the two groups to

search for differences that might serve as predictive factors for either operation. Perioperative findings were also analyzed. Results. The operation was accomplished by VATS in 40 patients (41%), and conversion to thoracotomy was necessary in 57 (59%). Significant predictive factors for conversion were a prolonged delay from diagnosis to operation, the presence of fever and of pleural thickness on computed tomography (CT) images. The 25 patients who presented with these three features were cured by thoracotomy. The operative time and postoperative complication rate were significantly higher for the thoracotomy patients. Conclusions. Some preoperative features can help the surgeon to better select patients for the appropriate operation. Delayed operation, fever, and pleural thickness can be used to predict the likelihood of conversion to thoracotomy.

5.2 Introduction

Surgical intervention is the treatment of choice for the advanced stages of pleural empyema, such as stage II (fibrinopurulent phase) and stage III (organizing phase). Video-assisted thoracic surgery (VATS) and thoracotomy are the mainstays in the surgical treatment of this disease[1–4]. VATS is less invasive than thoracotomy[3]; however, when used to cure empyema, performing a complete decortication through this approach is difficult. Thus, VATS is generally accepted as a very useful tool in the treatment of fibrinopurulent empyema[5], but the more the stage III empyema, the higher the VATS failure rate, necessitating further surgical intervention such as a thoracotomy with extensive decortication [2,4,6]. The issue of which preoperative findings can be used to select patients for initial VATS vs proceeding directly to a thoracotomy is rarely addressed. The American College of Chest Physicians consensus conference on the treatment of parapneumonic effusions stated that VATS and open operations are both acceptable approaches for managing patients with advanced-stage empyema, but no further details were provided about the clinical criteria for the selection of patients for either procedure[1]. No randomized studies comparing VATS and thoracotomy have been conducted. The retrospective nature of most studies precludes knowing on what basis VATS or thoracotomy was chosen, but it is likely that the clinical condition of the patient, pleural fluid characteristics, and radiographic features were considered[3,5,7,8]. The identification of a combination of preoperative findings that will allow surgeons to select a successful operation, either VATS or thoracotomy, could be of great interest in clinical practice. The aim

of this study was to determine which clinical and radiologic features might help to predict which patients will benefit from a successful VATS or which patients will require a thoracotomy. For this purpose, we retrospectively reviewed a series of patients with parapneumonic empyema who underwent successful VATS or thoracotomy and in which the operation began through VATS in all cases and was changed to a thoracotomy if needed.

5.3 Material and Methods

The University of Modena Institutional Review Board approved this study. The need for patient consent was waived because this was a retrospective study and because the patients were anonymized.

We retrospectively reviewed all adult patients operated on for parapneumonic empyema at our institution between 2005 and 2012. Only VATS and thoracotomy were considered. Patients with empyema associated with lung abscess or bronchiectasis and patients with tuberculous empyema were excluded.

Empyema was defined as frank pus aspirated from the pleural space, pleural fluid with positive results on microbiologic examinations, cloudy pleural fluid in the presence of multiloculated effusion, and systemic signs of infection, regardless of microbiologic findings. Thus, all patients in this study were confirmed to have empyema by diagnostic thoracentesis.

If frank pus was evacuated from the pleural space or if a multiloculated effusion was revealed by computed tomography (CT) scan, the patient was offered surgical treatment in the first instance. In cases of free-flowing effusion with positive microbiologic test results, an intercostal drainage procedure was first attempted as a treatment option. In these cases, our indications for surgical referral were persistent infection or unsatisfactory lung reexpansion detected on imaging studies. No fibrinolytic therapy was used for any patient. Compromised patients with high operative risk were treated conservatively with intercostal drainage and antibiotics.

Our policy since 2005 for surgical treatment has been to attempt VATS in every case, irrespective of the chronicity of the disease and of the clinical and radiologic features. The goals of the surgical treatment were complete evacuation of the infected material and restoration of lung expansion to obliterate any residual pleural space. Thus, all patients included in this study were initially operated on by VATS.

From 1 to 3 incisions were made, and an initial evaluation of the pleural space

was conducted. If lung adhesions were so tight and the pleural peel was so thick that the surgeon judged it was too difficult or hazardous to proceed entering the pleural space, an early conversion to a lateral muscle-sparing thoracotomy was undertaken. Conversely, if sufficient pleural space was found, a 3- access VATS was conducted, and evacuation of the infected fluid, disruptions of the loculations, and pleural debridement were performed.

An assessment was then made of the ability of the underlying parenchyma to reexpand by temporary inflation of the affected lung with positive pressure ventilation. If the lateral surfaces of the lung could reach the chest wall and the inferior surface could reach the diaphragm, the result was considered satisfactory. Otherwise, if the lung did not reexpand, then visceral pleural decortication was attempted, initially through VATS. If this approach was technically unfeasible or the result was unsatisfactory by direct observation, an intraoperative conversion to a lateral muscle-sparing thoracotomy was undertaken to perform a complete open decortication. Three chest tubes were placed at the end of both types of operation.

We analyzed the following clinical variables: age, sex, presence of fever at the time of operation, previous treatment with therapeutic thoracentesis or intercostal drainage, and delay from the onset of symptoms to the operation. The laboratory variables assessed were preoperative pleural fluid bacteriology, serum C-reactive protein (CRP) levels, and white blood cell (WBC) counts. The radiologic variables were all collected on CT scan images: amount of the effusion (expressed as > 50% or < 50% of the hemithorax), type of effusion (free-flowing or loculated; Fig 5.1), number of loculations (1, 2, or >2), pleural thickening (Fig 5.2), attenuation of pleural fluid collection (expressed in Hounsfield units), thickening of the extrapleural fat, and presence of air in the pleural space before any evacuation procedure. Pleural thickening was considered when pleura was more than 2 mm thick[9].

Success of the VATS or thoracotomy procedure was defined as infection resolution, radiographic lung reexpansion, and no additional drainage procedures, according to previously reported criteria[10]. Infection was considered as resolved when the fever disappeared, the WBC count and CRP levels normalized, and pleural fluid bacteriologic test results were negative. Chest roentgenograms before hospital discharge and at 1, 3, and 6 months postoperatively were compared with the preoperative roentgenograms, and the radiologic improvement was calculated using a 5-point percentage scale[10]. Complete (100%) to moderate (75%) improvement in lung reexpansion at any time during the follow-up was considered satisfactory.

The operating time, chest tube permanence, postoperative hospital stay, postop-

erative morbidity, and mortality were also recorded.

Statistical analysis was conducted using SPSS software (SPSS Inc, Chicago, IL). Descriptive analysis was expressed as frequency, mean, and standard deviation. Frequencies were compared with the χ^2 test for categoric variables, and continuous variables were compared using the t test and analysis of variance. Patients undergoing VATS and thoracotomy were compared in a univariate and multivariate analysis, performed by multiple logistic regression analysis. A p value of less than 0.05 was considered significant.

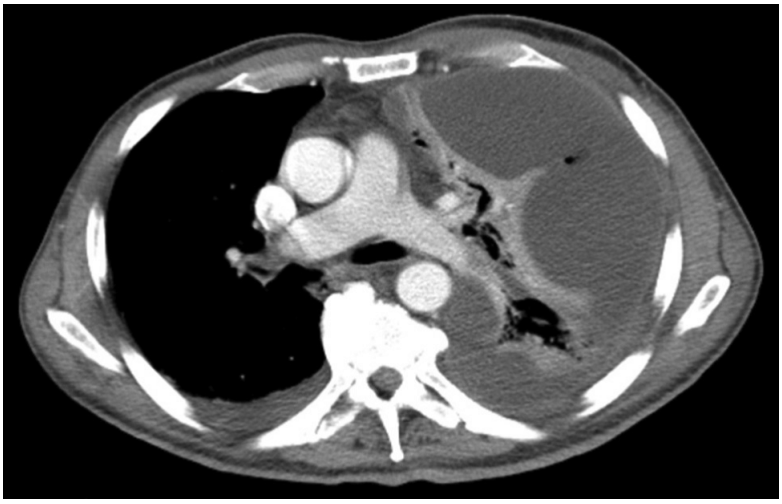

Figure 5.1: Computed tomography scan shows a multiloculated left pleural effusion

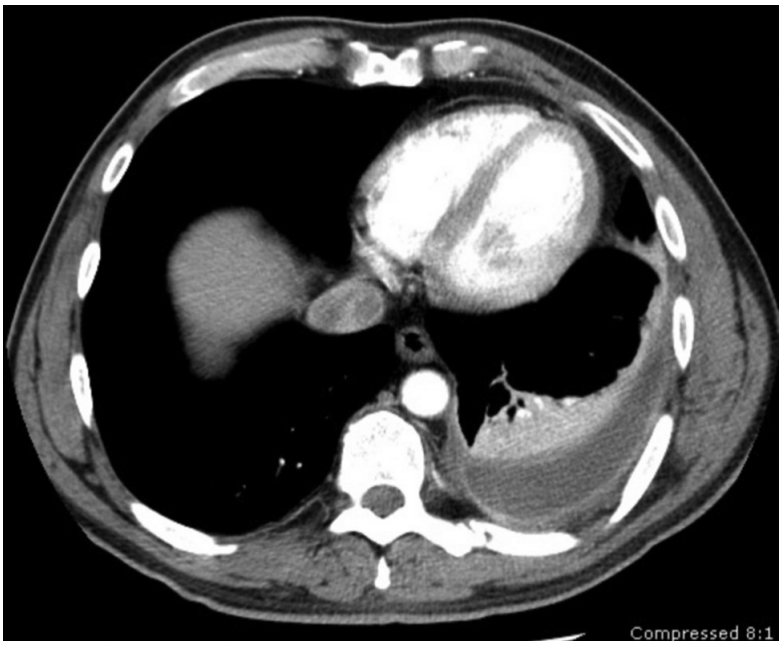

Figure 5.2: Computed tomography scan shows a left effusion with pleural thickening.

5.4 Results

Between January 2005 and December 2012, 100 adults underwent VATS or thoracotomy for parapneumonic empyema. The study excluded 3 patients: 1 patient, who underwent a thoracotomy, died of acute respiratory distress syndrome in the postoperative period; and the operation in 2 patients was unsuccessful because of persistent pleural space and uncontrolled infection, and a subsequent open-window thoracostomy was undertaken. The operation in the remaining 97 patients who entered the analysis was successful, with a 6-month minimum postoperative follow-up.

The operation was accomplished by VATS in 40 patients (41%), and a conversion to thoracotomy was necessary in 57 (59%). The reasons for conversion were the inability to enter the pleural space in 20 patients (35%) and incomplete lung reexpansion after debridement associated with the inability to perform a satisfactory thoracoscopic decortication in the remaining 37. Table 5.1 summarizes the preoperative characteristics of the patients.

Variable	No. (%) or Mean (Range)
Age, y	54 (21–83)
Sex	
Male	79 (81)
Female	18 (19)
Delay in operation, d	25 (5–92)
Fever	
Yes	77 (79)
No	20 (21)
WBC count, cells/μL	14,500 (4,800–52,000)
CRP level, mg/dL	18.3 (2.2–57.4)
Pleural fluid bacteriology	
Positive	25 (26)
Negative	72 (74)
Bacteria	
Gram-positive	16 (64)
Gram-negative	9 (36)
Previous drainage	
Yes	59 (61)
No	38 (39)
Amount of pleural fluid	
>50%	43 (44)
<50%	54 (56)
Type of effusion	
Free-flowing	23 (24)
Loculated	74 (76)
Loculations, No.	
1	11 (15)
2	21 (28)
>2	42 (57)
Pleural fluid density, HU	16.9 (0–31)
Pleural thickening	
Yes	44 (45)
No	53 (55)
Pleural thickening, mm	4.3 (2.1–7.5)
Extrapleural fat attenuation	
Yes	38 (39)
No	59 (61)
Intrapleural air	
Yes	12 (12)
No	73 (76)
Not applicable [a]	12 (12)

[a] Because a computed tomography scan was performed after evacuation procedure.

CRP = C-reactive protein; HU = Hounsfield units; WBC = white blood cell.

Table 5.1: Preoperative Features of the 97 Patients

The univariate analysis found that a longer delay from the onset of symptoms to the operation, the presence of fever, high levels of CRP, positive pleural fluid bacteriology, detection of loculations, and detection of pleural thickening were predictive factors of thoracotomy (Table 5.2).

Variable[b]	VATS (n = 40)	Thoracotomy (n = 57)	p Value
Delay in operation, d	19.5 (5–75)	29.5 (7–92)	0.007
Fever			<0.001
Yes	23 (57)	54 (95)	
No	17 (43)	3 (5)	
CRP level, mg/dL	15.8 (2.7–38.7)	20.1 (2.2–57.4)	0.04
Pleural fluid bacteriology			0.003
Positive	4 (10)	21 (37)	
Negative	36 (90)	36 (63)	
Type of effusion			0.029
Free-flowing	14 (35)	9 (16)	
Loculated	26 (65)	48 (84)	
Pleural thickening			0.003
Yes	11 (27.5)	33 (58)	
No	29 (72.5)	24 (42)	

[a] Only significantly different variables are shown. [b] Continuous data are shown as mean (range) and categoric data are shown as number (%).

CRP = C-reactive protein; VATS = video-assisted thoracoscopic surgery.

Table 5.2: Univariate Analysis: Comparison of Patients Undergoing Video-Assisted Thoracoscopic Surgery and Thoracotomy With Respect to Preoperative Featuresa

The multivariate analysis showed that long delay to operation, presence of fever, and detection of pleural thickening remained significant independent predictors of thoracotomy (Table 5.3). The rate of conversion to thoracotomy tended to increase with an increased delay to operation, especially after a treatment delay exceeding 20 days (Fig 5.3).

Risk Factor	OR (95% CI)[a]	p Value
Delay in operation	1.97 (1.12–3.48)	0.018
Fever: yes	28.17 (4.75–166.91)	0.000
C-creative protein	0.96 (0.56–1.65)	0.904
Bacteriology: positive	3.28 (0.69–15.52)	0.133
Type of effusion: loculated	1.05 (0.26–4.24)	0.945
Pleural thickening: yes	3.32 (1.01–10.79)	0.046

[a] An OR >1 indicates a risk factor for thoracotomy.

CI = confidence interval; OR = odds ratio.

Table 5.3: Multivariate Analysis of Independent Predictors of Thoracotomy

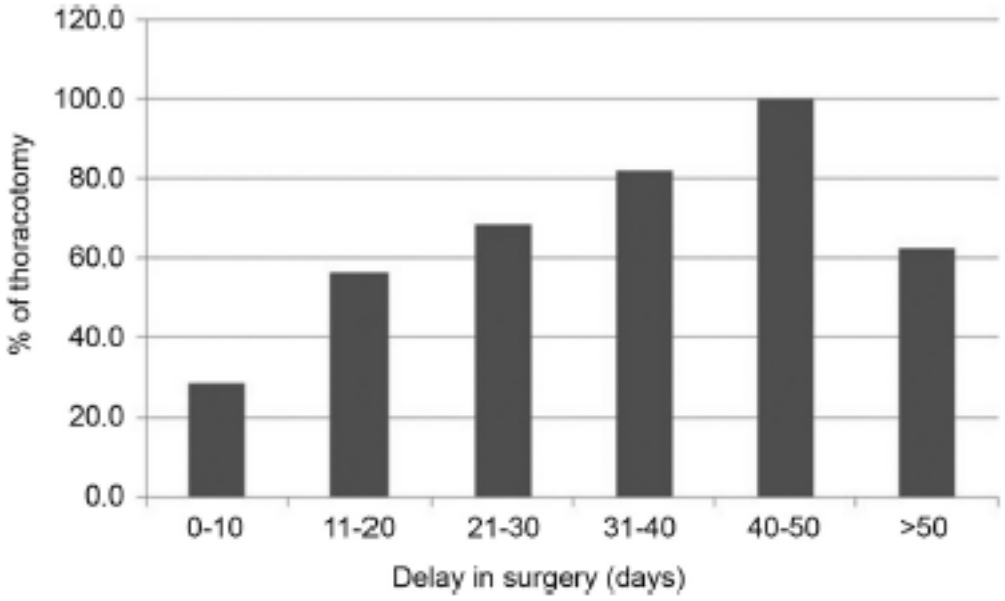

Figure 5.3: Rates of thoracotomy are shown according to the interval between the onset of symptoms and the operation.

The stratification of the significant variables showed that 83% of patients (30 of 36) with fever and a surgical delay of more than 20 days, 86% (30 of 35) with fever and pleural thickening, and 96% (25 of 26) with pleural thickening and a surgical delay of more than 20 days underwent thoracotomy. All 25 patients presenting with fever, pleural thickening, and who were operated on after a surgical delay of more than 20 days required a thoracotomy.

In the investigated period, the rate of successful VATS did not increase over time (Fig 5.4).

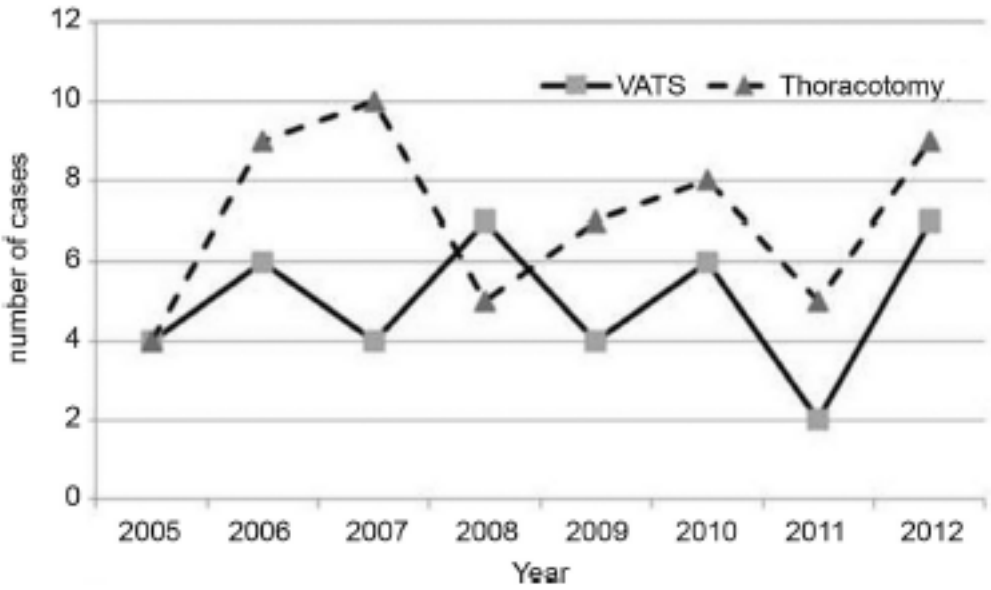

Figure 5.4: Number of patients undergoing surgical approach is shown by year of the study. (VATS ¼ video-assisted thoracoscopic surgery.)

The comparison of perioperative results between the two surgical approaches is reported in Table 4. No difference was found in operating time between VATS and thoracotomy when an early conversion was undertaken because of the inability to enter the pleural space (p ¼ 0.412), but a significant difference was observed between VATS and thoracotomy when the conversion was undertaken because of unsatisfactory lung reexpansion after VATS debridement (p ¼ 0.021). In the overall population, however, the operating time did not significantly increase with an increased delay to operation (Fig 5.5).

Variable[a]	VATS (n = 40)	Thoracotomy (n = 57)	*p* Value
Operating time, min	146 (90–210)	162 (80–255)	0.044
Chest tube duration, d	4.4 (2–12)	5.0 (2–40)	0.444
Post-op hospital stay, d	8.3 (3–30)	8.4 (3–44)	0.961
Complications			
Yes	5 (12.5)	18 (32)	0.030
No	35 (87.5)	39 (68)	

[a] Continuous data are shown as mean (range) and categoric data are shown as number (%).

VATS = video-assisted thoracoscopic surgery.

Table 5.4: Perioperative Results: Comparison Between Video- Assisted Thoracoscopic Surgery and Thoracotomy by Univariate Analysis

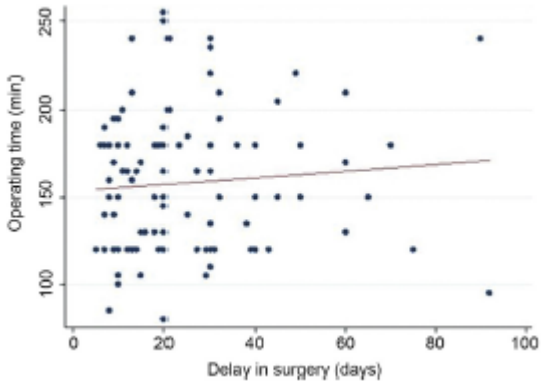

Figure 5.5: Correlation is shown between preoperative delay and operating time.

Complications occurred more frequently in thoracotomy patients, and air leak and bleeding were the most common complications.

5.5 Comment

Surgical intervention has shown superior success rates compared with simple drainage, with or without fibrinolysis, in the treatment of advanced-stage empyema[1,2,11]. That an early surgical treatment obtains better results in these cases is widely accepted[4,7,11]. Thus, we offered surgical intervention without attempting fibrinolysis first in patients with loculated empyema that did not resolve with a tube thoracostomy, if they were fit for an operation.

There is no consensus on which surgical operation, VATS or thoracotomy, should be the first-line procedure. VATS is less invasive[2–4], and several studies have demonstrated that it offers similar outcomes in resolution of empyema[3,4]. This finding has been observed particularly in the fibrinopurulent phase, when debridement can be sufficient to cure the disease and in which VATS represents the technique of choice[5,12,13]. The role of VATS remains controversial and limited in the organizing phase. Although some authors have reported satisfactory results with VATS in this advanced phase [6,12,14–16], a conversion to thoracotomy is needed in many patients. The inability to access the cavity with the thoracoscope because of strong adhesions between parietal and visceral pleura[14,16] or the inability to obtain an adequate pleural decortication to achieve lung reexpansion [5,13,15] represent the limits of VATS and the reasons for conversion. The latter was the main reason for conversion in our series.

In clinical practice, it is difficult to identify when an advanced stage disease will need a true decortication by large dissection of the restricted lung, requiring thoracotomy, or a simple blunt stripping of the pleural peel, which can be easily performed by VATS. This evaluation is usually performed at the time of operation [17].

In the American College of Chest Physicians consensus conference, large effusion, loculated effusion, thickened pleura, positive pleural fluid bacteriology, pus in the pleural cavity and pleural fluid pH of less than 7.20 were identified as predictors of the need for surgical drainage, but no further details were given[1]. Many surgeons consider primary thoracotomy more appropriate than VATS in patients with multiloculated empyema with thickened pleura and signs of lung entrapment or in patients with a long delay between onset of symptoms and referral to surgical intervention because they presume that a full pleural decortication will be needed [5,7,8,18]. Because in these studies the criteria for using each of the two approaches were different, no meaningful comparison can be made regarding preoperative variables between the two groups of patients. Moreover, a primary thoracotomy precludes knowing if a successful VATS might be performed in these patients. The experiences of authors who always begin operations with VATS and change to thoracotomy if necessary are useful for a more reliable analysis of the clinical predictors of a successful operation[6,14–17,19].

Conversion rates from VATS to thoracotomy are quite different among studies, ranging from 5.6% to 61% (Table 5.5). The policy to attempt VATS first in every patient may partly explain the highest rates. In fact, in our series we found a high

conversion rate (59%), as Roberts[17] and Waller and Rengarajan[14] also reported. However, other authors who have adopted this policy have reported significantly lower conversion rates [6,15,19]. Besides the surgical policy in approaching the disease, the variability in conversion rates must be explained by other factors, probably related to the stage of the disease.

Table 5 indicates when these preoperative predictors of conversion were investigated or reported. Unfortunately, the work of Lardinois and colleagues[18] was the only study specifically addressing this issue. In fact, the purpose of these studies was mainly to compare results and morbidity between VATS and thoracotomy, and the issue of preoperative features was secondary or not addressed. Moreover, most series included various forms of empyema other than parapneumonic such as postoperative, tuberculous, or posttraumatic empyema[5,8,12,13,15,17–19]. This heterogeneity makes the comparison among studies less reliable.

Our study included all features commonly accepted as descriptors of empyema[1,2,20], except for pleural fluid pH and ultrasonography findings. Although a low pleural fluid pH is traditionally considered to be predictive of empyema[1,7,8,11,18], the determination of pleural fluid pH was not routinely performed in our patients. Chest ultrasonography, in experienced hands, has recently been demonstrated to provide significant additional information[13,20]. However, ultrasonography was not routinely performed in our series. Conversely, CT is universally used to assess patients with empyema and may reveal several typical signs of the disease[20]. Although CT has not been shown to be completely reliable for differentiating the phases of empyema, it has a role in risk stratification and assessment of prognosis[1].

Delay in surgical intervention has been shown to be the most common predictor of conversion6[11,17–19,21] and was also an independent predictor of thoracotomy in our study. The probability of thoracotomy increased from 28% if the operation was performed within 10 days from the onset of symptoms to 81% if it was performed with a delay of between 30 and 40 days (Fig 5.3). This finding further demonstrates that an early surgical referral is mandatory for a successful VATS. Regarding the radiologic features, the only predictor of conversion was observed by Roberts[17], who found that only those patients diagnosed with “empyema” by the radiologist were more likely to require a thoracotomy. Conversely, Striffeler and colleagues[5] and Cassina and colleagues[13] concluded that the CT scan does not enable the selection of patients for successful VATS. In our series, loculated effusion and pleural thickening were both predictive of conversion, although only the second factor remained significant after multivariate analysis. We also measured the pleural thickening in

millimeters, but this variable did not correlate with the type of operation, perhaps due to sample scarcity (only 11 of 44 patients received VATS). Pleural fluid bacteriology was a predictor of conversion in some studies[11,18,22]; accordingly, we found positive bacteriology was a predictor of thoracotomy, but in the univariate analysis only. We could not investigate the effect of the type of bacteria on the conversion rate because of the scarcity of the samples. We found that fever was a strong predictor of conversion. Neither fever nor CRP levels have been previously shown to be predictors of unsuccessful VATS.

First Author	Pts[a] (No.)	Stage	Conversion Rate (%)	Preoperative Predictors
Landreneau [19]	76	II–III	17	Delay in operation
Striffeler [5]	67	II	28	None
Angelillo [22]	53	II	5.6	Gram-negative organisms
Cassina [13]	45	II–III	18	None
Waller [21]	39	II	59	Delay in operation
Waller [14]	36	III	41	Surgeon's experience
Roberts [17]	172	II–III	61.6	Delay in operation; "empyema" at CT
Kim [16]	70	II–III	7.1	Surgeon's experience
Lardinois [18]	178	II	44	Delay in operation; Gram-negative organisms
Luh [11]	234	II–III	17	Delay in operation, pus
Bilgin [7]	35	II	17	Not reported
Solaini [15]	110	II–III	8.2	Not reported
Cardillo [6]	185	II–III	5.9	Delay in surgery; stage III (no details)
Shahin [12]	81	II–III	8.6	Surgeon's experience; stage III (no details)
Tong [8]	420	II–III	11.4	Surgeon's experience
Current study	97	II–III	59	Delay in surgery, fever, pleural thickening

[a] Only studies with more than 30 patients were considered.

CT = computed tomography.

Table 5.5: Conversion Rate From Video-Assisted Thoracoscopic Surgery to Thoracotomy and Preoperative Predictors Of Conversion in Series of Empyema Patients Treated by Thoracoscopic Approach

Finally, other authors reported that "stage III" empyema was a predictor of conversion[6,12], but because no further clinical details were given, this finding may not be used to improve the selection of patients for either operation.

Some authors have reported that the conversion rate decreased with experience[8,12,14,16], primarily because decortication by VATS was subject to a learning curve. We did not observe this finding, perhaps because 10 years of experience had already been gained at the time of this study.

The high conversion rate in our series with respect to other series is probably explained by more advanced disease. In fact, the delay to surgical intervention was quite long (25 days on average), most patients had fever and loculated empyema,

and 45% of patients had pleural thickening. However, this high conversion rate was balanced by a high rate of success of 98% in our overall population treated with surgical intervention. This low failure rate, associated with a low mortality, shows that our algorithm (complete expansion of the lung after VATS debridement/decortication, or conversion to thoracotomy for a full pleural decortication) allows for complete drainage and prevents a residual pleural cavity.

Regarding postoperative findings, the difference in operating time between VATS and thoracotomy can be explained by the extra time required in attempting to perform unsuccessful VATS debridement/decortication. Other authors have reported prolonged operating times for thoracotomies[6,8,14,21]. Pleural decortication is undertaken mainly through thoracotomy, and this factor may explain the higher rate of complications after thoracotomy, which were mostly prolonged air leak and bleeding, as previously described[6,8,11,12,17]. However, those differences did not affect the duration of chest tube drainage or the hospital stay and did not increase the mortality rate. We believe that an increased risk of non-life-threatening complications can be acceptable as long as the mortality rate remains unchanged and the cure of the disease is warranted.

The main limitation of this study is its retrospective nature. The surgeon was not blinded to preoperative findings, introducing a bias in that the knowledge of predictors of VATS failure might have made the surgeon more ready to convert to thoracotomy. Moreover, different surgeons performed the operations. Another limitation is the absence of pleural fluid chemistry analyses and ultrasonography examinations. Studies including the chemistry analysis of pleural fluid and chest ultrasonography findings could be useful to provide further guidance for a better selection of the surgical approach for pleural empyema.

In conclusion, we have identified some clinical predictors of successful VATS or thoracotomy in the treatment of parapneumonic empyema. Patients presenting with fever and pleural thickening and who are operated on more than 20 days after the onset of symptoms will likely require a thoracotomy for appropriate treatment.

We believe that an optimal selection of patients for a successful operation has several advantages. First, the longer operative time due to late conversion after useless debridement can be avoided. Moreover, the patient will be prepared for a major operation, if a thoracotomy with extensive decortication is predicted. In addition, a useless VATS is avoided in patients for whom conversion cannot be undertaken because of poor conditions; in these patients, an open-window thoracostomy could be the approach of choice. Finally, the surgical team will be prepared for a

longer and more challenging operation in cases of predicted thoracotomy.

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Chapter 6

Conclusion

The importance of statistics in biomedical research is that we collect representative samples of subject, make measurements or observations on them, and then, by statistical analyses of data, draw inferences about the populations from which the samples were selected. Statistical inference allows to extend the results from a small group of observations (sample) to a much larger group of statistical units (population). The evidence to support the efficacy and safety for a specific drug derives from randomized controlled trials (RCTs)[20]. The ethical basis of a RCT is provided by the principle of equipoise, stating that the randomization is allowed when there is genuine uncertainty on the actual benefit of the intervention under study. An RCT ideally should permit an unbiased estimation of the treatment effect (e.g., overall survival (OS) or disease-free survival (DFS), through the comparison between an experimental treatment and a comparator, administrated in two separate arms.

My personal interest in this topic derives from the work during my PhD when I was involved in IRMA clinical trials, a randomized controlled trial aimed at comparing partial and accelerated irradiation with three-dimensional conformal radiotherapy (3D-CRT) vs. standard radiotherapy in women suffering from breast cancer with low risk of local recurrence and undergoing conservative surgery. The primary objective is to evaluate whether partial hypofractionated and accelerated irradiation of the sole surgical cavity is not inferior to postoperative irradiation with conventional fractionation of the entire breast as regards local control, measured in terms of incidence of ipsilateral recurrences as the first event. Survival analysis is part of inferential statistics and its peculiarity consists in relating a certain outcome or event with the time factor. Kaplan-Meier univariate analysis method is

the most widely used in clinical trials and cohort studies for the construction and comparison of survival curves.

In section 2, chapter 1 the methodology of randomized clinical trial is presented. The aim of this section is to explain what randomized controlled clinical trials are and to introduce the main concepts on data collection in clinical trials. The construction of an RCT to minimize the chance of an unreliable and biased conclusion falls into three categories: first, blinding of observer so that bias is reasonably controlled; second, presentation of data so that the opportunities for bias can be detected by the reader; and third, the proper use of statistical analyses so that unreliable conclusions are not drawn from unreliable data.

In section 3, chapter 1 we introduce the protocol of Randomized control trial. Every well-designed clinical trial requires a protocol. The study protocol can be viewed as a written agreement between the investigator, the participant, and the scientific community. In this section we present the contest provide the background, specify the objectives, and describe the design and organization of the trial. The protocol of a clinical trial must provide, in relation to the design of the study, its primary objective and the type of end-point chosen, the principles and statistical methods on which it will base the analysis of results, and in fact this one aspect crucial in the planning phase of a study.

Section 5-7, chapter 1 describes the most relevant existing statistical approaches usually used to analyze data from randomized controlled trials.

In section 7.8, chapter 1 the agreement test based on Cohen Kappa index have been applied has been introduced and applied to assess the correlation between two raters. In IRMA trial this test was used to compare the cosmetic results in patients with breast cancer with low risk of local recurrences in conservative surgery. The cosmetic evaluation was carried out by two independent assessors, such as radiologists and patients.

Chapter 1, section 8 shows the protocol of IRMA. This study aims at comparing partial and accelerated radiation with three-dimensional conformal radiotherapy (3DCRT) vs. standard radiotherapy in women aged $\geqq$ 49, ECOG 0-2, undergoing conservative breast surgery for invasive breast cancer, pT 1-2 (< 3 cm in diameter) pN0-N1 M0, unifocal, histologically negative resection margins ($\geq$ 2 mm) at first intervention or after subsequent widening.

When an RCT is designed to compare survival times (disease-free), updating the follow up becomes an important issue. Not doing it can critically affect the statistical analysis and interpretation of results.

As emerged from our analysis for the primary and secondary outcomes in Chapter 6, this phenomenon is quite common . At the moment the centers involved in the study are reporting the information on patients for whom the follow ups have not been updated.

In Chapter 1, section 9 the results of IRMA trial are presented confirming that randomization has worked since the two groups are well balanced in terms of prognostic factors.

In this section analyses on toxicity and cosmetic are also reported.

The length of follow-up is still relatively early, therefore patients will continue to be followed up to determine whether differences in bad cosmetics and toxicity will increase over time.

The study was planned to enroll 3302 patient, so far 2766 of them have been recruited (84%). On average 30 patients per month are enrolled and we expect to reach the plane sample size in one and half years.

Since the study is still enrolling patients can only present preliminary result and cannot provide final statement about the efficacy and safety of treatments under comparison.

However, the data so far analyzed suggest that the two groups are comparable in terms of baseline characteristics, that the quality of data is satisfactory and overall results are in line with expected ones.

In chapter 2, we presented the study of prevalence and diagnosis of vestibular disorders in children, a review of the literature.

In chapter 3, show the result of the incidence of clinical features of colorectal cancer patients in advanced age. This is a population-based (i.e., through a Registry) analysis that reports colorectal cancer characteristics, treatment and clinical outcome in geriatric patients over the age of 80 years.

In chapter 4, we present the EUROCARE high resolution study of disease presentation, treatment and survival for Italian colorectal cancer patients. This HR investigation provides an overview of the presentation, treatment and survival of Italian colorectal cancer cases diagnosed in 2003–05.

In Chapter 5, we present the study of preoperative predictions of successful surgical treatment in the management of parapneumonic empyema.

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