UNIVERSITA' DEGLI STUDI DI BRESCIA

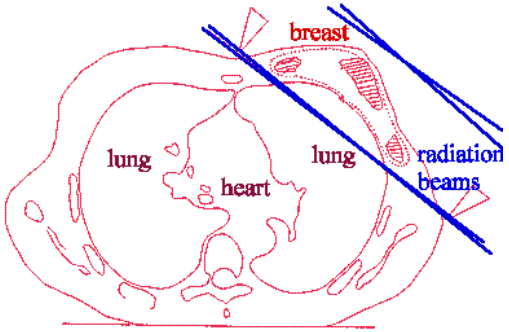
Recording Toxicity: the QUANTEC model

Michela Buglione di Monale – Nadia Pasinetti
Cattedra di Radioterapia

Brescia - September 30th 2011

Breast cancer radiotherapy

- Many treated volumes
- Different treatment modalities
- Many treatment techniques
- Many fractionation schemes



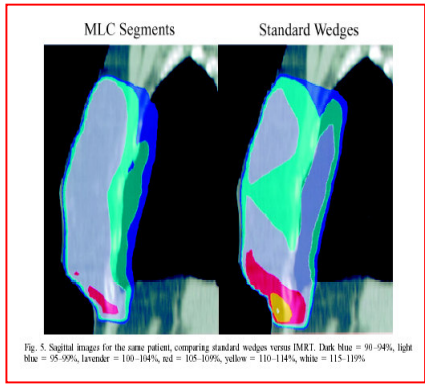


Fig. 5. Sagittal images for the same patient, comparing standard wedges versus IMRT. Dark blue = 90–94%, light blue = 95–99%, lavender = 100–104%, red = 105–109%, yellow = 110–114%, white = 115–119%

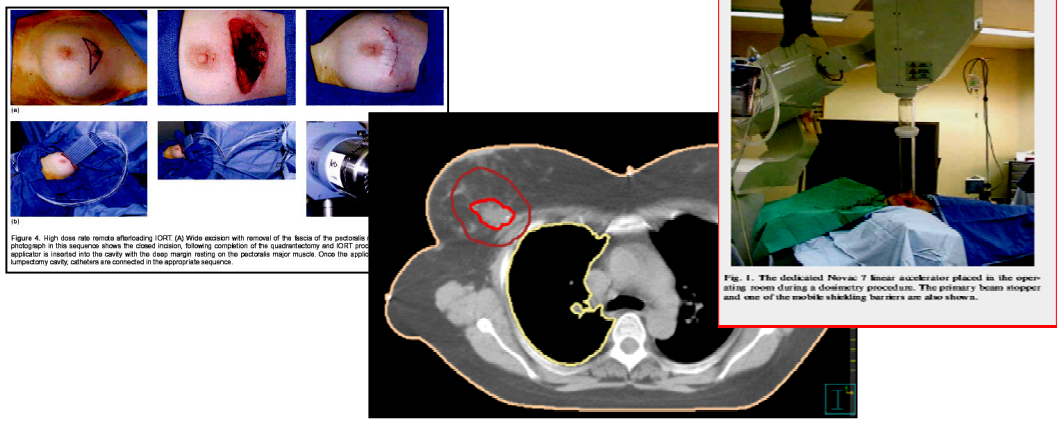
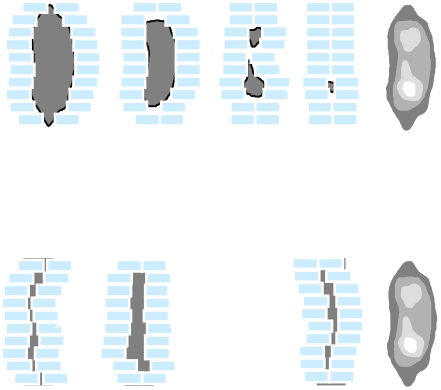


Figure 4. High dose rate remote afterloading IORT. (A) Wide excision with removal of the fascia of the pectoralis ... photograph in this sequence shows the closed incision, following completion of the quadrantectomy and IORT proc... applicator is inserted into the cavity with the deep margin resting on the pectoralis major muscle. Once the applic... lumpectomy cavity, catheters are connected in the appropriate sequence.

Fig. 1. The dedicated Novac 7 linear accelerator placed in the operating room during a dosimetry procedure. The primary beam stopper and one of the mobile shielding barriers are also shown.



An accurate toxicity evaluation is mandatory :

- To ***correlate*** and ***confirm (or not)*** the data derived from theoretical mathematical models (e.g., a/ß ratio) with adequate clinical data

- To ***collect data*** to guide therapeutic decisions

- To ***compare*** the effectiveness and toxicities of the different treatment options

An accurate toxicity evaluation is mandatory :

- To *correlate* and *confirm (or not)* the data derived from theoretical mathematical models (e.g., a/ß ratio) with adequate clinical data

- To *collect data* to guide therapeutic decisions

- To *compare* the effectiveness and toxicities of the different treatment options

EDITORIAL

THE OMEGA ON ALPHA AND BETA

IJROBP 81 (2): 319–320, 2011

ELI GLATSTEIN, M.D.

Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA

"OK, I confess: I have trouble with alpha/beta ratios, and I want to provoke some discussion.

The basic idea behind alpha/beta is a ratio of two different types of cell killing, essentially single hit and multiple hit types of radiation. This is what one gets with x-rays and the linear quadratic formula to explain a cell survival curve. That part is relatively understandable and straightforward.

The problem I have is when people propose to use alpha/betas for treatment of patients"

"Over the years, I have told many trainees that one can be an excellent clinical radiation oncologist and not necessarily know squat about alpha/beta. I believe that remains true today"

- **The mathematical models for the prediction of response and toxicity were often clearly not confirmed by clinical data**

CHART in head and neck cancer

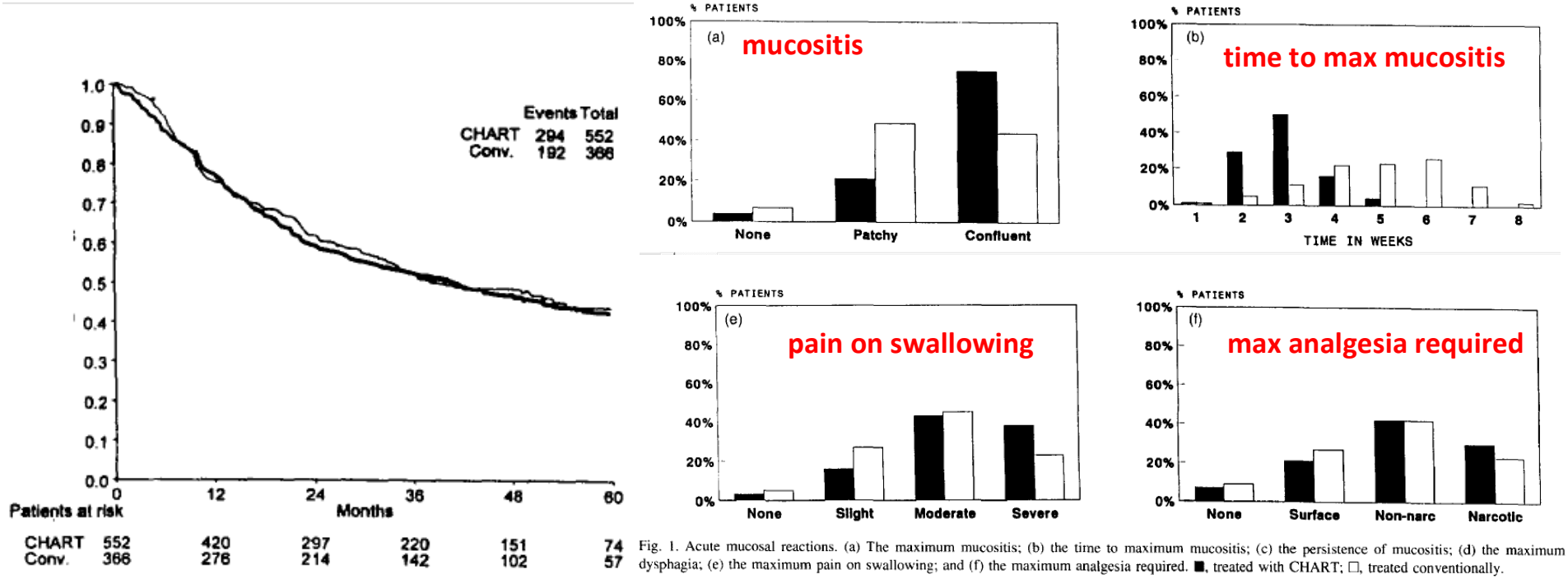


Fig. 1. Acute mucosal reactions. (a) The maximum mucositis; (b) the time to maximum mucositis; (c) the persistence of mucositis; (d) the maximum dysphagia; (e) the maximum pain on swallowing; and (f) the maximum analgesia required. ■, treated with CHART; □, treated conventionally.

Benzen et al Radiotherapy and Oncology (53): 219, 1999

Christie Hospital Breast Conservation Trial, 708 patients

	recurrence (%)	fat necrosis(n.)
Wide field, 6 MV Whole breast, 15 ff / 40 Gy (2.6 Gy / fr)	11 %	2
Local field, e- , 10 MeV 6 x 8 cm, 8 ff / 42.5 Gy (5.3 Gy / frazione)	15 %	10

Ribeiro et al Clinical Oncol 5(5): 278, 1993

• "Care should be taken when applying models, especially when clinical dose/volume parameters are beyond the range of data used to generate the model/parameters.

• Models and dose/volume recommendations are only as good as the data available.

• Typically, they are based on dose–volume histograms (DVHs).
• DVHs are not ideal representations of the 3D doses as they discard all organ-specific spatial information"

• "RT-induced normal tissue responses are fraction size dependent ….. "

• "….alfa/beta ratio is uncertain….."

Marks et al IJROBP 76(3) S10-19, 2010

•…..When ‘‘Emami’’ was published, most external RT was delivered with opposing fields, and shrinking field techniques—the normal tissue was irradiated with a fairly uniform fraction size.

•….use of sequential/concurrent chemotherapy/RT is increasing for many tumors…..

•….Modern techniques often use multiple beams (with or without concurrent boosts);

•…..the volume of normal tissue exposed to low doses is often increased and the dose is delivered at fraction sizes ranging from 0 to the prescribed fraction size.

•…..the duration follow-up is often inadequate to evaluate late toxicity

Marks et al IJROBP 76(3) S10-19, 2010

An accurate toxicity evaluation is mandatory :

- To *correlate* and *confirm (or not)* the data derived from theoretical mathematical models (e.g., α/β ratio) with adequate clinical data

- **To *collect data* to guide therapeutic decisions**

- To *compare* the effectiveness and toxicities of the different treatment options

the QUANTEC MODEL: IJROBP (76):3, 2010

Quantitative Analysis of Normal Tissue Effects in the Clinic

No skin
No breast

Organ-Specific Papers

1. **Brain**
2. **Optic Nerve/Chiasm**
3. **Brain Stem**
4. **Spinal Cord**
5. **Ear**
6. **Parotid**
7. **Larynx/Pharynx**
8. **Lung**
9. **Heart**
10. **Esophagus**
11. **Liver**
12. **Stomach/Small Bowel**
13. **Kidney**
14. **Bladder**
15. **Rectum**
16. **Penile Bulb**

Vision Papers
True Dose
Imaging
Biomarkers
Data Sharing
Lessons of QUANTEC

Each with 10 sections

1. **Clinical Significance**- Describes the clinical situations where the organ is irradiated, and the incidence/significance of organ injury.
2. **Endpoints**- Describes the different endpoints often considered when assessing injury, the impact of endpoint-selection on **the reported injury rates, the challenges/utilities of different endpoints, and the time course of organ injury.**
3. **Challenges Defining Volumes- Describes how the organ is typically defined (or segmented)** on treatment planning images. Includes a discussion of uncertainties/challenges in organ definition (e.g. changes in organ volume/shape during therapy), and the associated impact on DVH's and dose/volume/outcome analyses.
4. **Review of Dose/Volume Data**- A comprehensive summary of reported 3D dose/volume data for clinically-relevant outcomes.
5. **Factors Affecting Risk**- Other clinical factors affecting the risk of injury are noted (e.g. age, combined modality therapy, dose fractionation).
6. **Mathematical/Biological Models**- Models that have been used to relate 3D dose/volume data to clinical outcomes are summarized, along with associated model parameters, limitations and uncertainties.
7. **Special Situations**- Most of the data discussed relates to conventional fractionation. This section describes situations were the presented data/models may not apply (e.g. hypo-fractionation).
8. **Recommended Dose/Volume Limits**- The available information is condensed into meaningful dose/volume limits, with associated risk rates, to apply clinically.
9. **Future Toxicity Studies**- Describes areas in need of future study.
10. **Toxicity Scoring**- Recommendations on how to score organ injury.

How?: the QUANTEC MODEL

Quantitative Analysis of Normal Tissue Effects in the Clinic

Organ-Specific Papers

3. **Brain Stem**
4. **Spinal Cord**
5. **Ear**
6. **Parotid**
7. **Larynx/Pharynx**
8. **Lung**
9. **Heart**
10. **Esophagus**
11. **Liver**
12. **Stomach/Small Bowel**
13. **Kidney**
14. **Bladder**
15. **Rectum**
16. **Penile Bulb**

Vision Papers
True Dose
Imaging
Biomarkers
Data Sharing
Lessons of QUANTEC

Clinical aspects

Each with 10 sections

1. **Clinical Significance**- Describes the clinical situations where the organ is irradiated, and the incidence/significance of organ injury.
2. **Endpoints**- Describes the different endpoints often considered when assessing injury, the impact of endpoint-selection on **the reported injury rates, the challenges/utilities of different endpoints, and the time course of organ injury.**
3. **Challenges Defining Volumes- Describes how the organ is typically defined (or segmented)** on treatment planning images. Includes a discussion of uncertainties/challenges in organ definition (e.g. changes in organ volume/shape during therapy), and the associated impact on DVH's and dose/volume/outcome analyses.
4. **Review of Dose/Volume Data**- A comprehensive summary of reported 3D dose/volume data for clinically-relevant outcomes.
5. **Factors Affecting Risk**- Other clinical factors affecting the risk of injury are noted (e.g. age, combined modality therapy, dose fractionation).
6. **Mathematical/Biological Models**- Models that have been used to relate 3D dose/volume data to clinical outcomes are summarized, along with associated model parameters, limitations and uncertainties.
7. **Special Situations**- Most of the data discussed relates to conventional fractionation. This section describes situations were the presented data/models may not apply (e.g. hypo-fractionation).
8. **Recommended Dose/Volume Limits**- The available information is condensed into meaningful dose/volume limits, with associated risk rates, to apply clinically.
9. **Future Toxicity Studies**- Describes areas in need of future study.
10. **Toxicity Scoring**- Recommendations on how to score organ injury.

How?: the QUANTEC MODEL

Quantitative Analysis of Normal Tissue Effects in the Clinic

Organ-Specific Papers

1. **Brain**
2. **Optic Nerve/Chiasm**
3. **Brain Stem**
4. **Spinal Cord**
5. **Ear**
7. **Larynx/Pharynx**
8. **Lung**
9. **Heart**
10. **Esophagus**
11. **Liver**
12. **Stomach/Small Bowel**
13. **Kidney**
14. **Bladder**
15. **Rectum**
16. **Penile Bulb**

Vision Papers
True Dose
Imaging
Biomarkers
Data Sharing
Lessons of QUANTEC

OAR definition

Each with 10 sections

1. **Clinical Significance**- Describes the clinical situations where the organ is irradiated, and the incidence/significance of organ injury.
2. **Endpoints**- Describes the different endpoints often considered when assessing injury, the impact of endpoint-selection on **the reported injury rates, the challenges/utilities of different endpoints, and the time course of organ injury.**
3. **Challenges Defining Volumes**- Describes how the organ is **typically defined (or segmented)** on treatment planning images. Includes a discussion of uncertainties/challenges in organ definition (e.g. changes in organ volume/shape during therapy), and the associated impact on DVH's and dose/volume/outcome analyses.
4. **Review of Dose/Volume Data**- A comprehensive summary of reported 3D dose/volume data for clinically-relevant outcomes.
5. **Factors Affecting Risk**- Other clinical factors affecting the risk of injury are noted (e.g. age, combined modality therapy, dose fractionation).
6. **Mathematical/Biological Models**- Models that have been used to relate 3D dose/volume data to clinical outcomes are summarized, along with associated model parameters, limitations and uncertainties.
7. **Special Situations**- Most of the data discussed relates to conventional fractionation. This section describes situations were the presented data/models may not apply (e.g. hypo-fractionation).
8. **Recommended Dose/Volume Limits**- The available information is condensed into meaningful dose/volume limits, with associated risk rates, to apply clinically.
9. **Future Toxicity Studies**- Describes areas in need of future study.
10. **Toxicity Scoring**- Recommendations on how to score organ injury.

How?: the QUANTEC MODEL

Quantitative Analysis of Normal Tissue Effects in the Clinic

Organ-Specific Papers

1. **Brain**
2. **Optic Nerve/Chiasm**
3. **Brain Stem**
4. **Spinal Cord**
5. **Ear**
6. **Parotid**
7. **Larynx/Pharynx**

Data from literature

10. **Esophagus**
11. **Liver**
12. **Stomach/Small Bowel**
13. **Kidney**
14. **Bladder**
15. **Rectum**
16. **Penile Bulb**

Vision Papers
True Dose
Imaging
Biomarkers
Data Sharing
Lessons of QUANTEC

Each with 10 sections

1. **Clinical Significance**- Describes the clinical situations where the organ is irradiated, and the incidence/significance of organ injury.
2. **Endpoints**- Describes the different endpoints often considered when assessing injury, the impact of endpoint-selection on **the reported injury rates, the challenges/utilities of different endpoints, and the time course of organ injury.**
3. **Challenges Defining Volumes- Describes how the organ is typically defined (or segmented)** on treatment planning images. Includes a discussion of uncertainties/challenges in organ definition (e.g. changes in organ volume/shape during therapy), and the associated impact on DVH's and dose/volume/outcome analyses.
4. **Review of Dose/Volume Data**- A comprehensive summary of reported 3D dose/volume data for clinically-relevant outcomes.
5. **Factors Affecting Risk**- Other clinical factors affecting the risk of injury are noted (e.g. age, combined modality therapy, dose fractionation).
6. **Mathematical/Biological Models**- Models that have been used to relate 3D dose/volume data to clinical outcomes are summarized, along with associated model parameters, limitations and uncertainties.
7. **Special Situations**- Most of the data discussed relates to conventional fractionation. This section describes situations were the presented data/models may not apply (e.g. hypo-fractionation).
8. **Recommended Dose/Volume Limits**- The available information is condensed into meaningful dose/volume limits, with associated risk rates, to apply clinically.
9. **Future Toxicity Studies**- Describes areas in need of future study.
10. **Toxicity Scoring**- Recommendations on how to score organ injury.

How?: the QUANTEC MODEL

Quantitative Analysis of Normal Tissue Effects in the Clinic

Organ-Specific Papers

1. **Brain**
2. **Optic Nerve/Chiasm**
3. **Brain Stem**
4. **Spinal Cord**
5. **Ear**
6. **Parotid**
7. **Larynx/Pharynx**
8. **Lung**
14. **Bladder**
15. **Rectum**
16. **Penile Bulb**

Vision Papers
True Dose
Imaging
Biomarkers
Data Sharing
Lessons of QUANTEC

Each with 10 sections

1. **Clinical Significance**- Describes the clinical situations where the organ is irradiated, and the incidence/significance of organ injury.
2. **Endpoints**- Describes the different endpoints often considered when assessing injury, the impact of endpoint-selection on **the reported injury rates, the challenges/utilities of different endpoints, and the time course of organ injury.**
3. **Challenges Defining Volumes- Describes how the organ is typically defined (or segmented)** on treatment planning images. Includes a discussion of uncertainties/challenges in organ definition (e.g. changes in organ volume/shape during therapy), and the associated impact on DVH's and dose/volume/outcome analyses.
4. **Review of Dose/Volume Data**- A comprehensive summary of reported 3D dose/volume data for clinically-relevant outcomes.
5. **Factors Affecting Risk**- Other clinical factors affecting the risk of injury are noted (e.g. age, combined modality therapy, dose fractionation).
6. **Mathematical/Biological Models**- Models that have been used to relate 3D dose/volume data to clinical outcomes are summarized, along with associated model parameters, limitations and uncertainties.
7. **Special Situations**- Most of the data discussed relates to conventional fractionation. This section describes situations were the presented data/models may not apply (e.g. hypo-fractionation).
8. **Recommended Dose/Volume Limits**- The available information is condensed into meaningful dose/volume limits, with associated risk rates, to apply clinically.
9. **Future Toxicity Studies**- Describes areas in need of future study.
10. **Toxicity Scoring**- Recommendations on how to score organ injury.

Data about factors affecting the risk and about models used to predict the damage

How?: the QUANTEC MODEL

Quantitative Analysis of Normal Tissue Effects in the Clinic

Organ-Specific Papers

1. **Brain**
2. **Optic Nerve/Chiasm**
3. **Brain Stem**
4. **Spinal Cord**
5. **Ear**
6. **Parotid**
7. **Larynx/Pharynx**
8. **Lung**
9. **Heart**
10. **Esophagus**
11. **Liver**
12. **Stomach/Small Bowel**
13. **Kidney**
14. **Bladder**

Imaging
Biomarkers
Data Sharing
Lessons of QUANTEC

Each with 10 sections

1. **Clinical Significance**- Describes the clinical situations where the organ is irradiated, and the incidence/significance of organ injury.
2. **Endpoints**- Describes the different endpoints often considered when assessing injury, the impact of endpoint-selection on **the reported injury rates, the challenges/utilities of different endpoints, and the time course of organ injury.**
3. **Challenges Defining Volumes- Describes how the organ is typically defined (or segmented)** on treatment planning images. Includes a discussion of uncertainties/challenges in organ definition (e.g. changes in organ volume/shape during therapy), and the associated impact on DVH's and dose/volume/outcome analyses.
4. **Review of Dose/Volume Data**- A comprehensive summary of reported 3D dose/volume data for clinically-relevant outcomes.
5. **Factors Affecting Risk**- Other clinical factors affecting the risk of injury are noted (e.g. age, combined modality therapy, dose fractionation).
6. **Mathematical/Biological Models**- Models that have been used to relate 3D dose/volume data to clinical outcomes are summarized, along with associated model parameters, limitations and uncertainties.
7. **Special Situations**- Most of the data discussed relates to conventional fractionation. This section describes situations were the presented data/models may not apply (e.g. hypo-fractionation).
8. **Recommended Dose/Volume Limits**- The available information is condensed into meaningful dose/volume limits, with associated risk rates, to apply clinically.
9. **Future Toxicity Studies**- Describes areas in need of future study.
10. **Toxicity Scoring**- Recommendations on how to score organ injury.

Recommendations about dose/volume limits

How? the QUANTEC MODEL

Quantitative Analysis of Normal Tissue Effects in the Clinic

Organ-Specific Papers

1. **Brain**
2. **Optic Nerve/Chiasm**
3. **Brain Stem**
4. **Spinal Cord**
5. **Ear**
6. **Parotid**
7. **Larynx/Pharynx**
8. **Lung**
9. **Heart**
10. **Esophagus**
11. **Liver**
12. **Stomach/Small Bowel**
13. **Kidney**
14. **Bladder**
15. **Rectum**
16. **Penile Bulb**

Vision Papers

Data Sharing
Lessons of QUANTEC

Each with 10 sections

1. **Clinical Significance**- Describes the clinical situations where the organ is irradiated, and the incidence/significance of organ injury.
2. **Endpoints**- Describes the different endpoints often considered when assessing injury, the impact of endpoint-selection on **the reported injury rates, the challenges/utilities of different endpoints, and the time course of organ injury.**
3. **Challenges Defining Volumes- Describes how the organ is typically defined (or segmented)** on treatment planning images. Includes a discussion of uncertainties/challenges in organ definition (e.g. changes in organ volume/shape during therapy), and the associated impact on DVH's and dose/volume/outcome analyses.
4. **Review of Dose/Volume Data**- A comprehensive summary of reported 3D dose/volume data for clinically-relevant outcomes.
5. **Factors Affecting Risk**- Other clinical factors affecting the risk of injury are noted (e.g. age, combined modality therapy, dose fractionation).
6. **Mathematical/Biological Models**- Models that have been used to relate 3D dose/volume data to clinical outcomes are summarized, along with associated model parameters, limitations and uncertainties.
7. **Special Situations**- Most of the data discussed relates to conventional fractionation. This section describes situations were the presented data/models may not apply (e.g. hypo-fractionation).
8. **Recommended Dose/Volume Limits**- The available information is condensed into meaningful dose/volume limits, with associated risk rates, to apply clinically.
9. **Future Toxicity Studies**- Describes areas in need of future study.
10. **Toxicity Scoring**- Recommendations on how to score organ injury.

Future studies

How?: the QUANTEC MODEL

Quantitative Analysis of Normal Tissue Effects in the Clinic

Organ-Specific Papers

1. **Brain**
2. **Optic Nerve/Chiasm**
3. **Brain Stem**
4. **Spinal Cord**
5. **Ear**
6. **Parotid**
7. **Larynx/Pharynx**
8. **Lung**
9. **Heart**
10. **Esophagus**
11. **Liver**
12. **Stomach/Small Bowel**
13. **Kidney**
14. **Bladder**
15. **Rectum**
16. **Penile Bulb**

Vision Papers
True Dose
Imaging

Each with 10 sections

1. **Clinical Significance**- Describes the clinical situations where the organ is irradiated, and the incidence/significance of organ injury.
2. **Endpoints**- Describes the different endpoints often considered when assessing injury, the impact of endpoint-selection on **the reported injury rates, the challenges/utilities of different endpoints, and the time course of organ injury.**
3. **Challenges Defining Volumes- Describes how the organ is typically defined (or segmented)** on treatment planning images. Includes a discussion of uncertainties/challenges in organ definition (e.g. changes in organ volume/shape during therapy), and the associated impact on DVH's and dose/volume/outcome analyses.
4. **Review of Dose/Volume Data**- A comprehensive summary of reported 3D dose/volume data for clinically-relevant outcomes.
5. **Factors Affecting Risk**- Other clinical factors affecting the risk of injury are noted (e.g. age, combined modality therapy, dose fractionation).
6. **Mathematical/Biological Models**- Models that have been used to relate 3D dose/volume data to clinical outcomes are summarized, along with associated model parameters, limitations and uncertainties.
7. **Special Situations**- Most of the data discussed relates to conventional fractionation. This section describes situations were the presented data/models may not apply (e.g. hypo-fractionation).
8. **Recommended Dose/Volume Limits**- The available information is condensed into meaningful dose/volume limits, with associated risk rates, to apply clinically.
9. **Future Toxicity Studies**- Describes areas in need of future study.
10. **Toxicity Scoring**- Recommendations on how to score organ injury.

Toxicity scoring

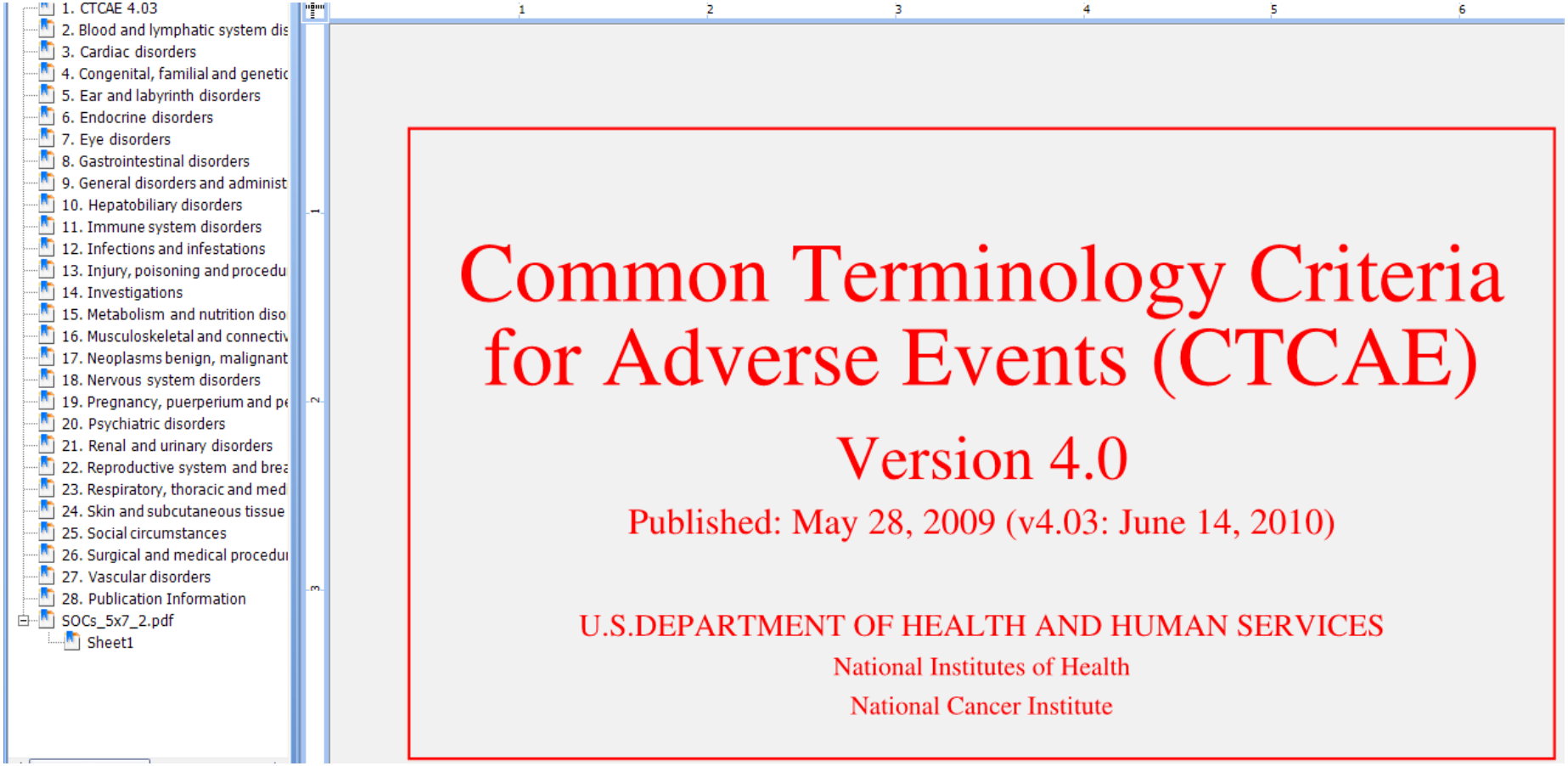
RTOG acute toxicity

Tissue	G 1	G 2	G 3	G 4
Skin	Follicular, faint or dull erythema / epilation / dry desquamation / decreased sweating	Tender or bright erythema, patchy moist desquamation / moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Lung	Mild symptoms of dry cough or dyspnea on exertion	Persistent cough requiring narcotic, antitussive agents / dyspnea with minimal effort but not at rest	Severe cough unresponsive to narcotic antitussive agent or dyspnea at rest / clinical or radiological evidence of acute pneumonitis / intermittent oxygen or steroids may be required	Severe respiratory insufficiency / continuous oxygen or assisted ventilation
Heart	Asymptomatic but objective evidence of EKG changes or pericardial abnormalities without evidence of other heart disease	Symptomatic with EKG changes and radiological findings of congestive heart failure or pericardial disease / no specific treatment required	Congestive heart failure, angina pectoris, pericardial disease responding to therapy	Congestive heart failure, angina pectoris, pericardial disease, arrhythmias not responsive to nonsurgical measures

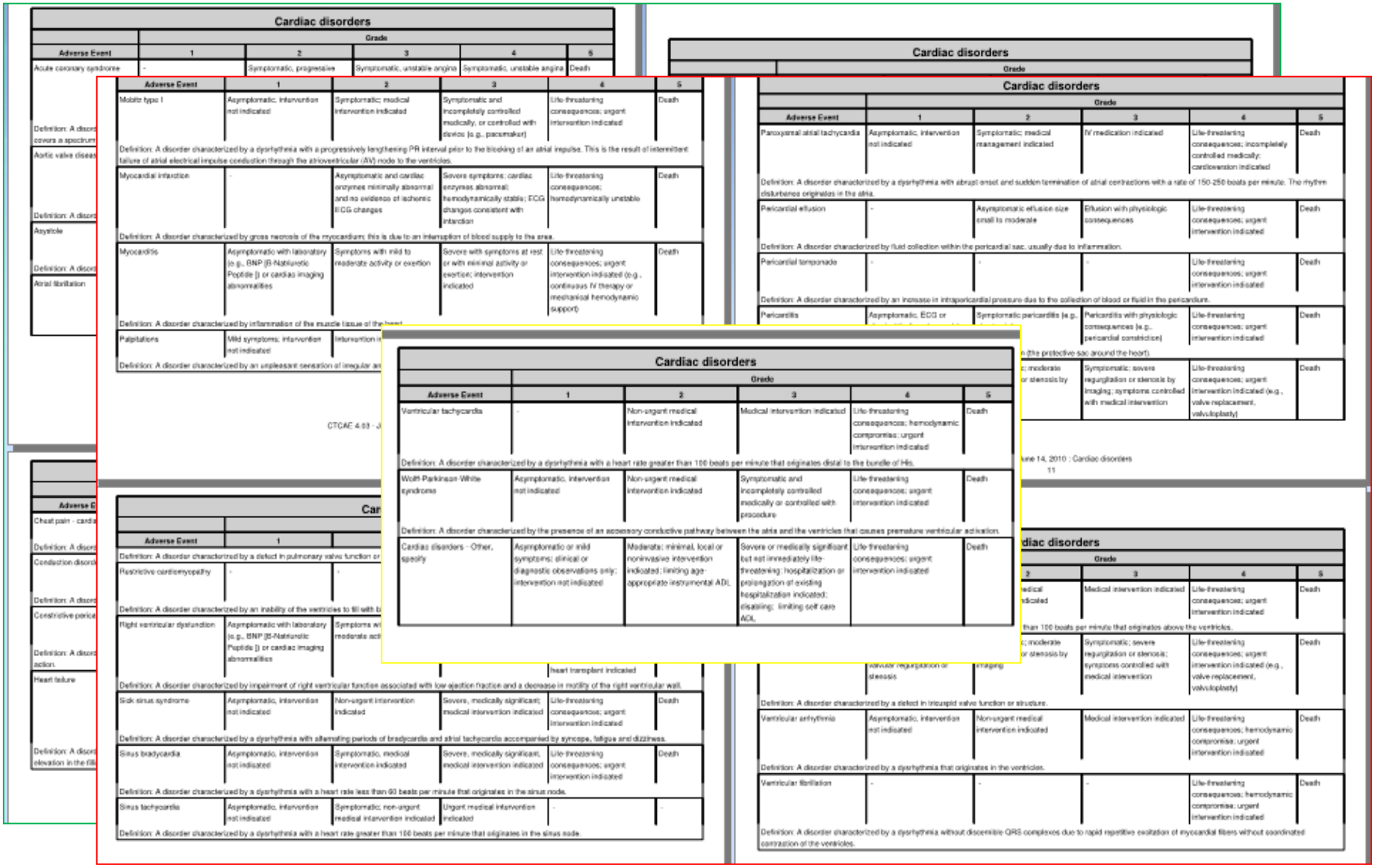
RTOG late toxicity

Tissue	G 1	G 2	G 3	G 4
Skin	Slight atrophy; pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration
Lung	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 oxygen / assisted ventilation
Heart	Asymptomatic or mild symptoms; transient T wave inversion & ST changes; sinus tachy > 110 (at rest)	Moderate angina on effort; mild pericarditis; normal heart size; persistent abnormal T wave and ST changes; low ORS	Severe angina; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; EKG abnormalities	Tamponade / severe heart failure; severe constrictive pericarditis

CTCAE 4.0 2010



CTCAE 4.0 2010 – heart



Cardiac disorders

Adverse Event	Grade 1	2	3	4	5
Acute coronary syndrome	-	Symptomatic, progressive	Symptomatic, unstable angina	Symptomatic, unstable angina	Death
Definition: A disord... covers a spectrum					
Aortic valve disease					
Definition: A disord...					
Asystole					
Definition: A disord...					
Atrial fibrillation					

Cardiac disorders

Adverse Event	Grade 1	2	3	4	5
Mobitz type I	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a progressively lengthening PR interval prior to the blocking of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.					
Myocardial infarction	-	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction	Life-threatening consequences; hemodynamically unstable	Death
Definition: A disorder characterized by gross necrosis of the myocardium; this is due to an interruption of blood supply to the area.					
Myocarditis	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Definition: A disorder characterized by inflammation of the muscle tissue of the heart.					
Palpitations	Mild symptoms; intervention not indicated	Intervention ...			
Definition: A disorder characterized by an unpleasant sensation of irregular an...					

Cardiac disorders

Adverse Event	Grade 1	2	3	4	5
Paroxysmal atrial tachycardia	Asymptomatic, intervention not indicated	Symptomatic; medical management indicated	IV medication indicated	Life-threatening consequences; incompletely controlled medically; cardioversion indicated	Death
Definition: A disorder characterized by a dysrhythmia with abrupt onset and sudden termination of atrial contractions with a rate of 150-250 beats per minute. The rhythm disturbance originates in the atria.					
Pericardial effusion	-	Asymptomatic; effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fluid collection within the pericardial sac, usually due to inflammation.					
Pericardial tamponade	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in intrapericardial pressure due to the collection of blood or fluid in the pericardium.					
Pericarditis	Asymptomatic; ECG or ...	Symptomatic pericarditis (e.g., ...	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; urgent intervention indicated	Death
... (this protective sac around the heart).					
...: moderate ... or stenosis by ...			Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death

...une 14, 2010 : Cardiac disorders
11

Cardiac disorders

Adverse Event	Grade 1	2	3	4	5
Ventricular tachycardia	-	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates distal to the bundle of His.					
Wolff-Parkinson-White syndrome	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with procedure	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the presence of an accessory conductive pathway between the atria and the ventricles that causes premature ventricular activation.					
Cardiac disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

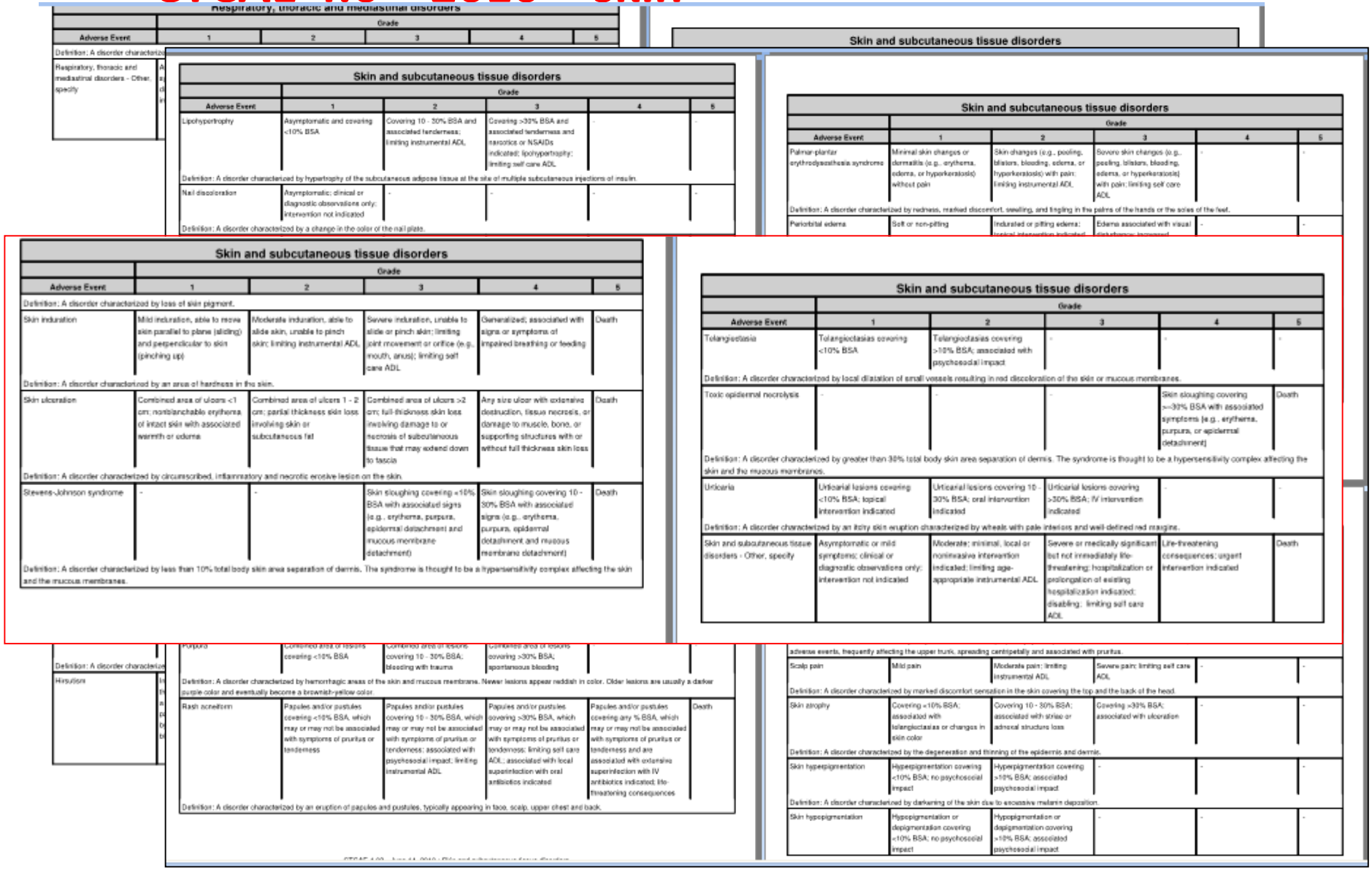
Car...

Adverse Event	Grade 1	...	...	...	...
Definition: A disorder characterized by a defect in pulmonary valve function or ...					
Restrictive cardiomyopathy	-	-			
Definition: A disorder characterized by an inability of the ventricles to fill with b...					
Right ventricular dysfunction	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms wi... moderate act...		heart transplant indicated	
Definition: A disorder characterized by impairment of right ventricular function associated with low ejection fraction and a decrease in motility of the right ventricular wall.					
Sick sinus syndrome	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	Severe, medically significant; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with alternating periods of bradycardia and atrial tachycardia accompanied by syncope, fatigue and dizziness.					
Sinus bradycardia	Asymptomatic, intervention not indicated	Symptomatic, medical intervention indicated	Severe, medically significant; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate less than 60 beats per minute that originates in the sinus node.					
Sinus tachycardia	Asymptomatic, intervention not indicated	Symptomatic; non-urgent medical intervention indicated	Urgent medical intervention indicated	-	-
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates in the sinus node.					

...diac disorders

...	Grade ...	...	3	4	5
...edical ...dicated			Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
...than 100 beats per minute that originates above the ventricles.					
...: moderate ... or stenosis by ...			Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in tricuspid valve function or structure.					
Ventricular arrhythmia	Asymptomatic; intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia that originates in the ventricles.					
Ventricular fibrillation	-	-	-	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without discernible QRS complexes due to rapid repetitive excitation of myocardial fibers without coordinated contraction of the ventricles.					

CTCAE 4.0 2010 – skin



Respiratory, thoracic and mediastinal disorders

Adverse Event	Grade 1	2	3	4	5
Definition: A disorder characterize					
Respiratory, thoracic and mediastinal disorders - Other, specify	A				

Skin and subcutaneous tissue disorders

Adverse Event	Grade 1	2	3	4	5
Lipohypertrophy	Asymptomatic and covering <10% BSA	Covering 10 - 30% BSA and associated tenderness; limiting instrumental ADL	Covering >30% BSA and associated tenderness and narcotics or NSAIDs indicated; lipohypertrophy; limiting self care ADL		
Definition: A disorder characterized by hypertrophy of the subcutaneous adipose tissue at the site of multiple subcutaneous injections of insulin.					
Nail discoloration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by a change in the color of the nail plate.					

Skin and subcutaneous tissue disorders

Adverse Event	Grade 1	2	3	4	5
Definition: A disorder characterized by loss of skin pigment.					
Skin induration	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration, unable to slide or pinch skin; limiting (joint movement or orifice (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by an area of hardness in the skin.					
Skin ulceration	Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss	Death
Definition: A disorder characterized by an circumscribed, inflammatory and necrotic erosive lesion on the skin.					
Stevens-Johnson syndrome	-	-	Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Skin sloughing covering 10 - 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Death
Definition: A disorder characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.					

Skin and subcutaneous tissue disorders

Adverse Event	Grade 1	2	3	4	5
Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL	-	-
Definition: A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet.					
Periorbital edema	Soft or non-pitting	Indurated or pitting edema; topical intervention indicated	Edema associated with visual disturbance; intervention indicated	-	-

Skin and subcutaneous tissue disorders

Adverse Event	Grade 1	2	3	4	5
Telangiectasia	Telangiectasias covering <10% BSA	Telangiectasias covering >10% BSA; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by local dilatation of small vessels resulting in red discoloration of the skin or mucous membranes.					
Toxic epidermal necrolysis	-	-	-	Skin sloughing covering >=30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment)	Death
Definition: A disorder characterized by greater than 30% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.					
Urticaria	Urticarial lesions covering <10% BSA; topical intervention indicated	Urticarial lesions covering 10 - 30% BSA; oral intervention indicated	Urticarial lesions covering >30% BSA; IV intervention indicated	-	-
Definition: A disorder characterized by an itchy skin eruption characterized by wheals with pale interiors and well-defined red margins.					
Skin and subcutaneous tissue disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Skin and subcutaneous tissue disorders

Adverse Event	Grade 1	2	3	4	5
Definition: A disorder characterize					
Hirsutism	H				
Purpura	Combined area of lesions covering <10% BSA	Combined area of lesions covering 10 - 30% BSA; bleeding with trauma	Combined area of lesions covering >30% BSA; spontaneous bleeding		
Definition: A disorder characterized by hemorrhagic areas of the skin and mucous membrane. Newer lesions appear reddish in color. Older lesions are usually a darker purple color and eventually become a brownish-yellow color.					
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.					

Skin and subcutaneous tissue disorders

Adverse Event	Grade 1	2	3	4	5
adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus.					
Scalp pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the skin covering the top and the back of the head.					
Skin atrophy	Covering <10% BSA; associated with telangiectasias or changes in skin color	Covering 10 - 30% BSA; associated with striae or adnexal structure loss	Covering >30% BSA; associated with ulceration	-	-
Definition: A disorder characterized by the degeneration and thinning of the epidermis and dermis.					
Skin hyperpigmentation	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized by darkening of the skin due to excessive melanin deposition.					
Skin hypopigmentation	Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact	Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact	-	-	-

CTCAE 4.0 2010 – lung

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Adult respiratory distress syndrome	-	-	Present with radiologic findings; intubation not indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by progressive and life-threatening pulmonary distress in the absence of an underlying pulmonary condition, usually following major trauma or surgery.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Atelectasis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., dyspnea, cough); medical intervention indicated (e.g., chest physiotherapy, suctioning);	Oxygen indicated; hospitalization or elective operative intervention indicated (e.g., stent, laser)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Bronchial stricture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., rhonchi or wheezing) but without respiratory distress; medical intervention indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Chylothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thoracentesis or tube drainage indicated	Severe symptoms; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent	Death

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Hoarseness	Mild or intermittent voice change; fully understandable; self-resolving	Moderate or persistent voice changes; may require occasional repetition but	Severe voice changes including predominantly whispered speech	-	-

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Laryngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a narrowing of the laryngeal airway.					
Laryngopharyngeal dysesthesia	Mild symptoms; no anxiety; intervention not indicated	Moderate symptoms; mild anxiety, but no dyspnea; short duration of observation and or anxiolytic indicated; limiting instrumental ADL	Severe symptoms; dyspnea and swallowing difficulty; limiting self care ADL	Life-threatening consequences	Death
Definition: A disorder characterized by an uncomfortable persistent sensation in the area of the laryngopharynx.					
Laryngospasm	-	Transient episode; intervention not indicated	Recurrent episodes; noninvasive intervention indicated (e.g., breathing technique, pressure point massage)	Persistent or severe episodes associated with syncope; urgent intervention indicated (e.g., fiberoptic laryngoscopy, intubation, botox injection)	Death
Definition: A disorder characterized by paroxysmal spasmodic muscular contraction of the vocal cords.					
Mediastinal hemorrhage	Radiologic evidence only; minimal symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by bleeding from the mediastinum.					
Nasal congestion	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Associated with bloody nasal discharge or epistaxis	-	-
Definition: A disorder characterized by obstruction of the nasal passage due to mucosal edema.					
Pharyngeal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the pharynx and another organ or anatomic site.					
Pharyngeal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pharynx.					
Pharyngeal mucositis	Endoscopic findings only; minimal symptoms with	Moderate pain and analgesics indicated; altered oral intake; instrumental ADL	Severe pain; unable to adequately ailment or hydrate orally; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
					ucous membrane of the pharynx.

+ others 8 pages

SOMA-LENT 1995 breast

	GRADE 1	GRADE 2	GRADE 3	GRADE 4	SCORING
Subjective					
Pain	Occasional & minimal Hypersensation, Pruritus	Intermittent & tolerable	Persistent & intense	Refractory & excruciating	____
Objective					
Edema	Asymptomatic	Symptomatic	Secondary dysfunction		____
Fibrosis* / Fat necrosis	Barely palpable increased density	Definite increased density and firmness	Very marked density, retraction and fixation		____
Telangiectasia	< 1 cm^2	1 cm^2 - 4 cm^2	> 4 cm^2		____
Lymphedema, arm (circumference)	2 cm - 4 cm increase	> 4 cm - 6 cm increase	> 6 cm increase	Useless arm, angiosarcoma	____
Retraction/Atrophy**	10% - 25%	> 25% - 40 %	> 40% - 75%	Whole breast	____
Ulcer	Epidermal only, ≤ 1 cm^2	Dermal, > 1 cm^2	Subcutaneous	Bone exposed, necrosis	____
Management					
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention	____
Edema			Medical intervention	Surgical intervention/ mastectomy	____
Lymphedema, arm		Elevate arm, elastic stocking	Compression wrapping, intensive physiotherapy	Surgical intervention/ amputation	____
Atrophy				Surgical intervention/ mastectomy	____
Ulcer		Medical intervention	Surgical intervention, wound debridement	Surgical intervention/ mastectomy	____

1995

* Compare exposed area to contralateral non-irradiated skin according to defined parameters ** Volume loss due to surgery +/or RT. (compared to opposite breast)

Instructions

Score the 12 SOM parameters with 1 - 4

(Score = 0 if there are no toxicities)

Total the scores and divide by 12

LENT Score: _____

Analytic		
Photographs	Assessment of skin changes as atrophy, retraction or fibrosis, ulcer	Y/N Date:
Tape measure	Assessment of breast size and forearm diameter	Y/N Date:
Mammogram	Assessment of skin thickness and breast density	Y/N Date:
CT/MRI	Assessment of breast size, fat atrophy, and fibrosis density	Y/N Date:

IJROBP 31(5) 1049-1091 (1995)

SOMA-LENT 1995 heart

	GRADE 1	GRADE 2	GRADE 3	GRADE 4	SCORING
Subjective					
Angina pectoris	Occasional, only with intense exertion	With moderate exertion	With mild exertion	At rest	____
Pericardial Pain	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating	____
Palpitation	Occasional	Intermittent	Persistent	Refractory	____
Dyspnea	SOB on intense exertion	SOB on mild exertion	SOB at rest, limits all activity	Prevents any physical activity	____
Pedal edema		Asymptomatic	Symptomatic	Prevents daily activities	____
Objective					
Pedal edema	1+	2+	3+	4+	____
Cardiomegaly	Minimal enlargement of cardiosilhouette (ECS)	ECS without pulmonary congestion	ECS with minimal pulmonary congestion	ECS with frank pulmonary edema	____
Cardiac dysrhythmia	Occasional, asymptomatic	Intermittent ECG changes	Persistent ECG changes	Refractory	____
Myocardial CHF	Asymptomatic decline of resting ejection fraction by ≤20% of baseline	Decline of resting ejection fraction by >20% of baseline	Reversible CHF	Irreversible CHF	____
Myocardial ischemia	Abnormal stress test NL resting EKG	Asymptomatic, ST & T wave changes without stress test	Angina without evidence for infarction	Acute myocardial infarction	____
Pericardial disease	Asymptomatic effusion	Rub, chest pain, ECG changes	Tamponade	Constriction	____
Management					
Pain (pericarditis)	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Coronary artery bypass	____
Angina	Present but no therapy	Nitroglycerin PRN	Long acting agents	Coronary artery bypass	____
Pericardial disease		Present but no therapy	Pericardiocenthesis	Pericardiectomy	____
Cardiac dysrhythmia			Medical intervention	Requires monitoring or cardioversion	____
Myocardial infarction			Medical intervention	Coronary bypass	____
Myocardial CHF			Medical intervention	Cardiac transplant	____

Instructions
Score the 17 SOM parameters with 1 - 4

(Score = 0 if there are no toxicities)

Total the scores and divide by 17

LENT Score:

_____

9901

IJROBP 31(5) 1049-1091 (1995)

SOMA-LENT 1995 lung

	GRADE 1	GRADE 2	GRADE 3	GRADE 4	SCORING
Subjective					
Cough	Occasional	Intermittent	Persistent	Refractory	____
Dyspnea	Breathless on intense exertion	Breathless on mild exertion	Breathless at rest, limits all activities	Prevents any physical activity	____
Chest pain/discomfort	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating	____
Objective					
Pulmonary fibrosis	Radiological abnormality	Patchy dense abnormalities on radiograph	Dense confluent radiographic changes limited to radiation field	Dense fibrosis, severe scarring & major retraction of normal lung	____
Lung function	10% - 25% reduction of respiration volume and/or diffusion capacity	> 25% - 50% reduction of respiration volume and/or diffusion capacity	> 50% - 75% reduction of respiration volume and/or diffusion capacity	> 75% reduction of respiration volume and/or diffusion capacity	____
Management					
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention	____
Cough		Non-narcotic	Narcotic, intermittent corticosteroids	Respirator, continuous corticosteroids	____
Dyspnea		Occasional O_2	Continuous O_2		____

Instructions
Score the 8 SOM parameters with 1 - 4

(Score = 0 if there are no toxicities)

Total the scores and divide by 8

LENT Score: _____

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

1069

IJROBP 31(5) 1049-1091 (1995)

REPORTING: IS IT A SOLVED PROBLEM?

No!

Hoeller et al IJROBP 55(4): 1013 (2003)

CLINICAL INVESTIGATION **Normal Tissue**

INCREASING THE RATE OF LATE TOXICITY BY CHANGING THE SCORE? A COMPARISON OF RTOG/EORTC AND LENT/SOMA SCORES

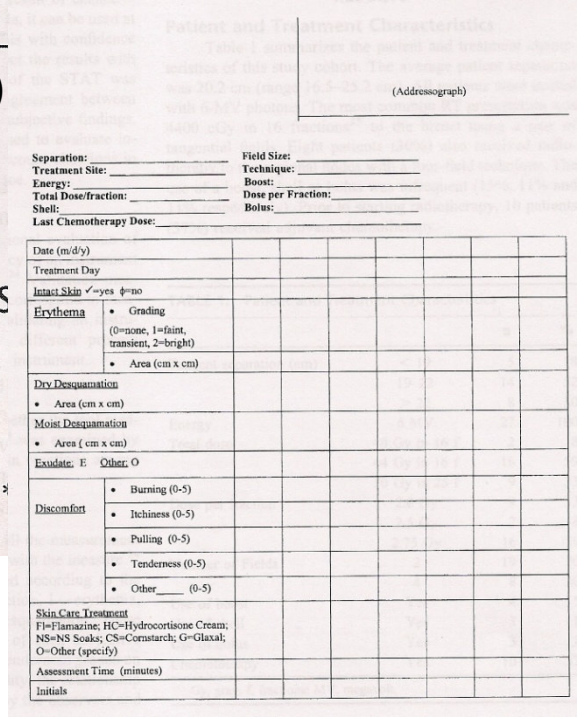
ULRIKE HOELLER, M.D., SILKE TRIBIUS, M.D., ANTJE KUHLMEY, M.D., KAI GRADER, FABIAN FEHLAUER, M.D., AND WINFRIED ALBERTI, PH.D.

ORIGINAL ARTICLE

Berthelet et al Am Journ Clin Oncol 27(6): 626 (2004)

Preliminary Reliability and Validity Testing of a New Skin Toxicity Assessment Tool (STAT) in Breast Cancer Patients Undergoing Radiotherapy

Eric Berthelet, MD,§ Pauline T. Truong, MDCM,*§ Karin Musso, RN,† Vickie Grant, RTT,† Winkle Kwan, MBBS,*§ Veronika Moravan, MSc,‡ Kelly Patterson, RTT,† and Ivo A. Olivotto, MD**



(Addressograph)

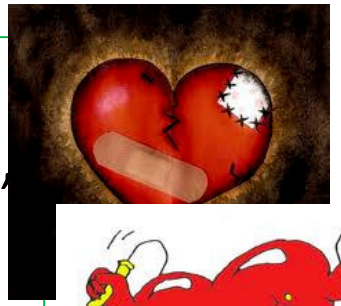
Separation: Field Size:
Treatment Site: Technique:
Energy: Boost:
Total Dose/fraction: Dose per Fraction:
Shell: Bolus:
Last Chemotherapy Dose:

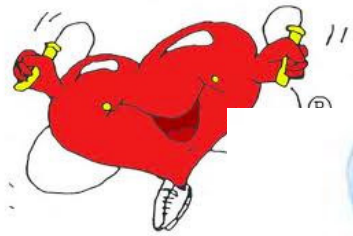
Date (m/d/y)								
Treatment Day								
Intact Skin ✓=yes ϕ=no								
Erythema	• Grading (0=none, 1=faint, transient, 2=bright)							
	• Area (cm x cm)							
Dry Desquamation	• Area (cm x cm)							
Moist Desquamation	• Area (cm x cm)							
Exudate: E Other: O								
Discomfort	• Burning (0-5)							
	• Itchiness (0-5)							
	• Pulling (0-5)							
	• Tenderness (0-5)							
	• Other____ (0-5)							
Skin Care Treatment Fl=Flamazine; HC=Hydrocortisone Cream; NS=NS Soaks; CS=Cornstarch; G=Glaxal; O=Other (specify)								
Assessment Time (minutes)								
Initials								

- **Which are the organs of interest?**
- **Which are the informations in QUANTEC for each of these?**
- **Which are the most important data about these organs?**

- **heart**

radiation-related heart disease (RRHD) → pericarditis, pericardial fibrosis, diffuse myocardial fibrosis, and coronary artery disease (CAD)





- **lung**

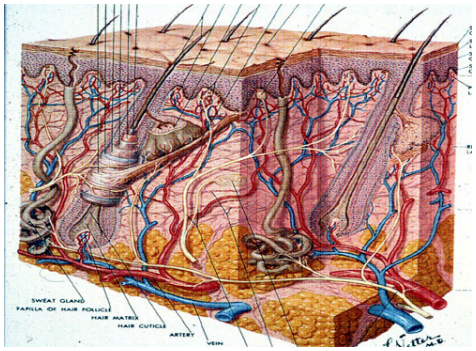
Early → pneumonitis

Late → fibrosis

- **skin**

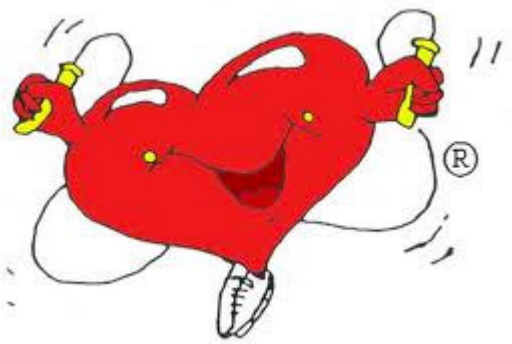
Early → dryness, epilation, pigmentation changes, and erythema

Sub-acute → Dry desquamation



Late →atrophy and fibrosis; pigmentation changes; telangiectasias

Heart



radiation-related heart disease (RRHD) → pericarditis, pericardial fibrosis, diffuse myocardial fibrosis, and coronary artery disease (CAD)

QUANTEC MODEL: heart

Clinical aspects

- **Pericardial disease**
- **Ischemic heart disease** → > RR of cardiac morbidity in old series treated with old RT tecniques
- **Congestive heart failure**
- **Valvular disease**

Gagliardi et al IJROBP 76(3) S77-85 (2010)

QUANTEC MODEL: heart

Clinical aspects

- **Pericardial disease**
- **Ischemic heart disease** → > RR of cardiac morbidity in old series treated with old RT tecniques
- **Congestive heart failure**
- **Valvular disease**

OAR definition

- **challenges in defining volumes** (entire heart, pericardium, left ventricle , coronary arteries)

Gagliardi et al IJROBP 76(3) S77-85 (2010)

QUANTEC MODEL: heart

Clinical aspects

- **Pericardial disease**
- **Ischemic heart disease** → > RR of cardiac morbidity in old series treated with old RT tecniques
- **Congestive heart failure**
- **Valvular disease**

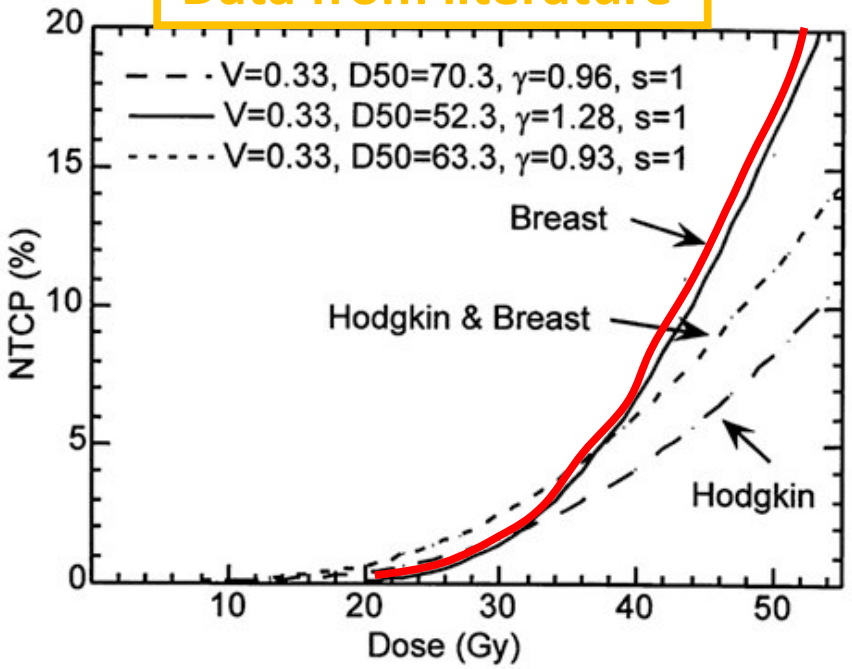
OAR definition

- **challenges in defining volumes** (entire heart, pericardium, left ventricle , coronary arteries)

Data about factors affecting the risk and about models used to predict the damage

- **damage related to dose and irradiated volumes → minimize the irradiated heart volume**

Data from literature



Gagliardi et al IJROBP 76(3) S77-85 (2010)

QUANTEC MODEL: heart

Clinical aspects

- **Pericardial disease**
- **Ischemic heart disease** → > RR of cardiac morbidity in old series treated with old RT tecniques
- **Congestive heart failure**
- **Valvular disease**

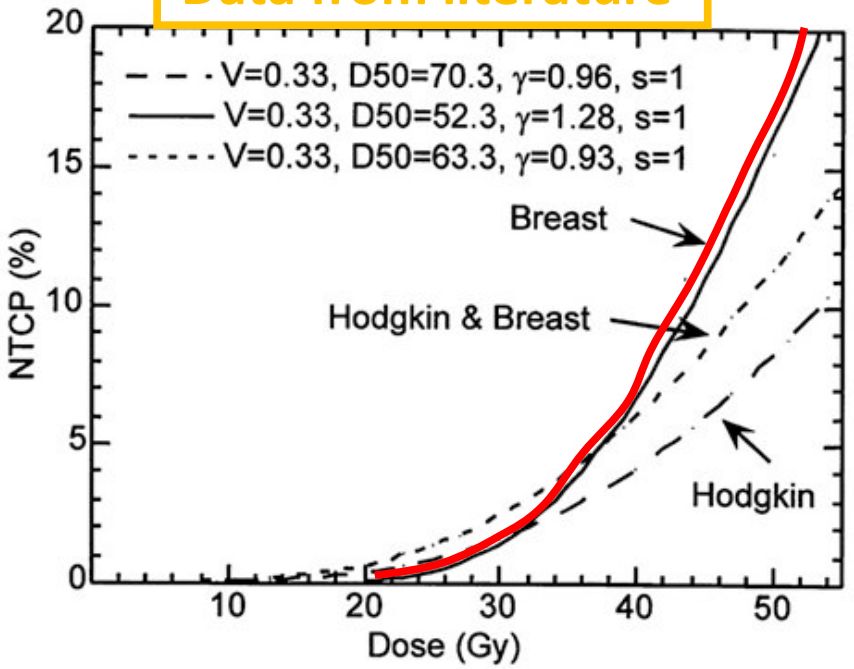
OAR definition

- **challenges in defining volumes** (entire heart, pericardium, left ventricle , coronary arteries)

Data about factors affecting the risk and about models used to predict the damage

- **damage related to dose and irradiated volumes** → **minimize the irradiated heart volume**

Data from literature



Recommendations about dose/volume limits

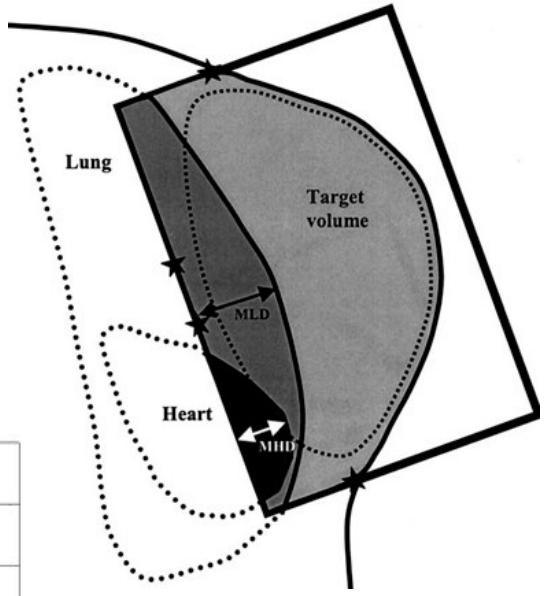
- V25Gy < 10% → <1% probability of cardiac mortality

Gagliardi et al IJROBP 76(3) S77-85 (2010)

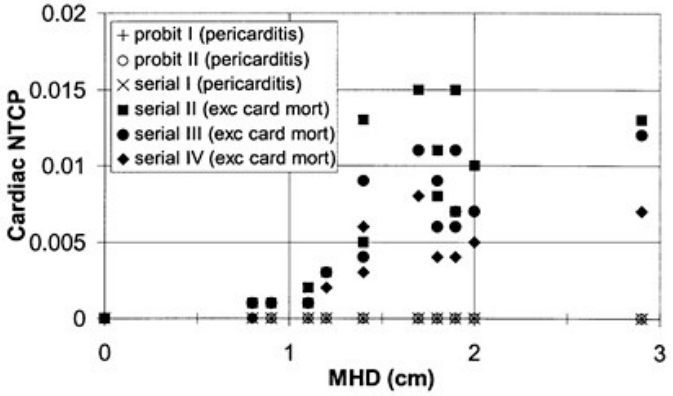
Not only QUANTEC: heart

Cardiac and pulmonary doses and complication probabilities in standard and conformal tangential irradiation in conservative management of breast cancer

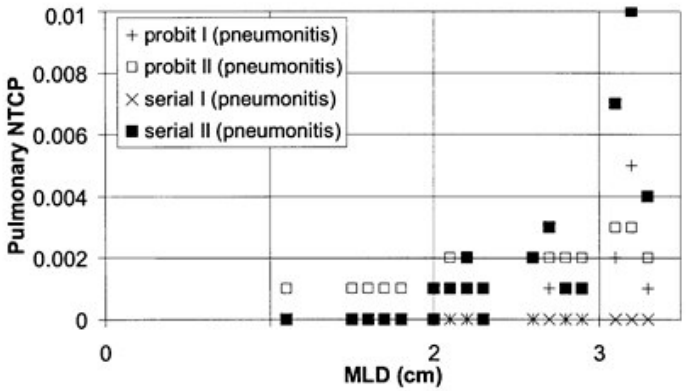
- **Different NTCP model/parameter combinations give different predictions for the risks radiation-induced cardiac and pulmonary morbidity;**
- **Good agreement when small volumes of OAR were irradiated**



< 1 cm



<2-2.5 cm

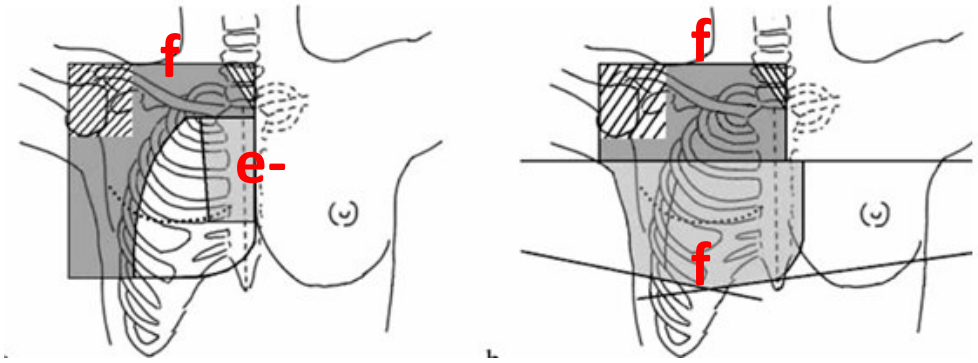


1‰ risk for cardiac and pulmonary morbidity

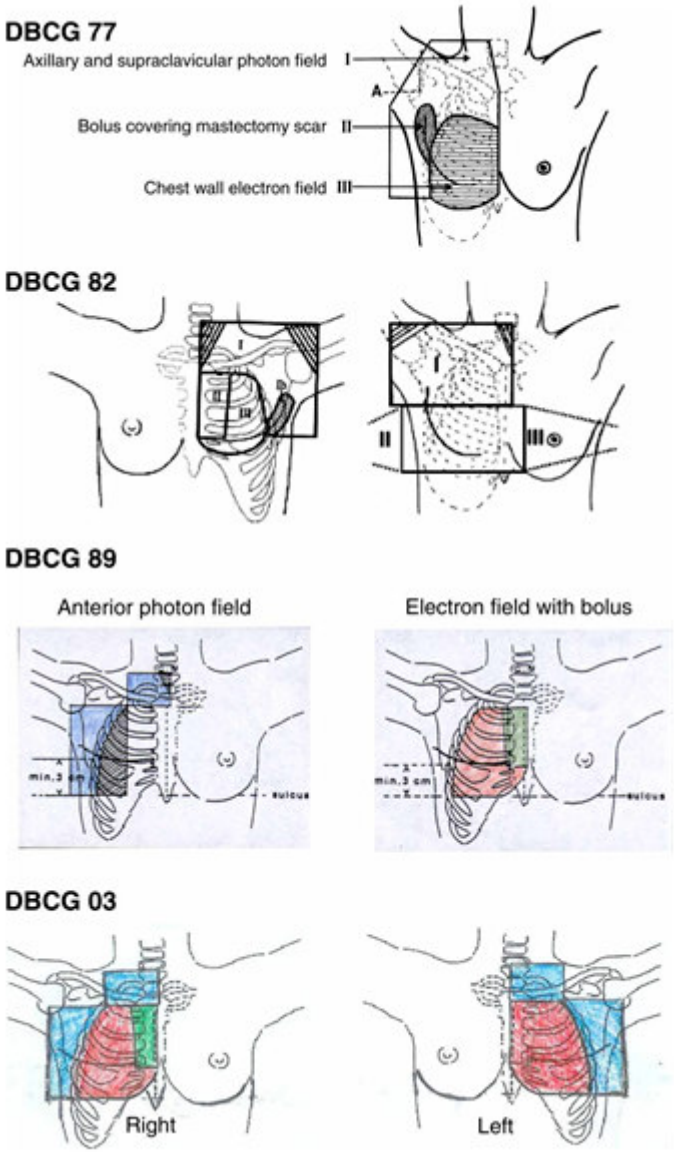
Muren et al Radiot and Oncol 62: 173 (2002)

Not only QUANTEC: heart

Strong relation between RT techniques/volumes and doses to OAR



Thomsen Acta Oncol 47: 654 (2008)



M. Overgaard Acta Oncol 47: 639 (2008)

Editorial

Radiation-induced heart morbidity after adjuvant radiotherapy of early breast cancer – Is it still an issue?

Birgitte Offersen *, Inger Højris, Marie Overgaard

Department of Oncology, Aarhus University Hospital, Aarhus C, Denmark

Radiot and Oncol 100: 157 (2011)

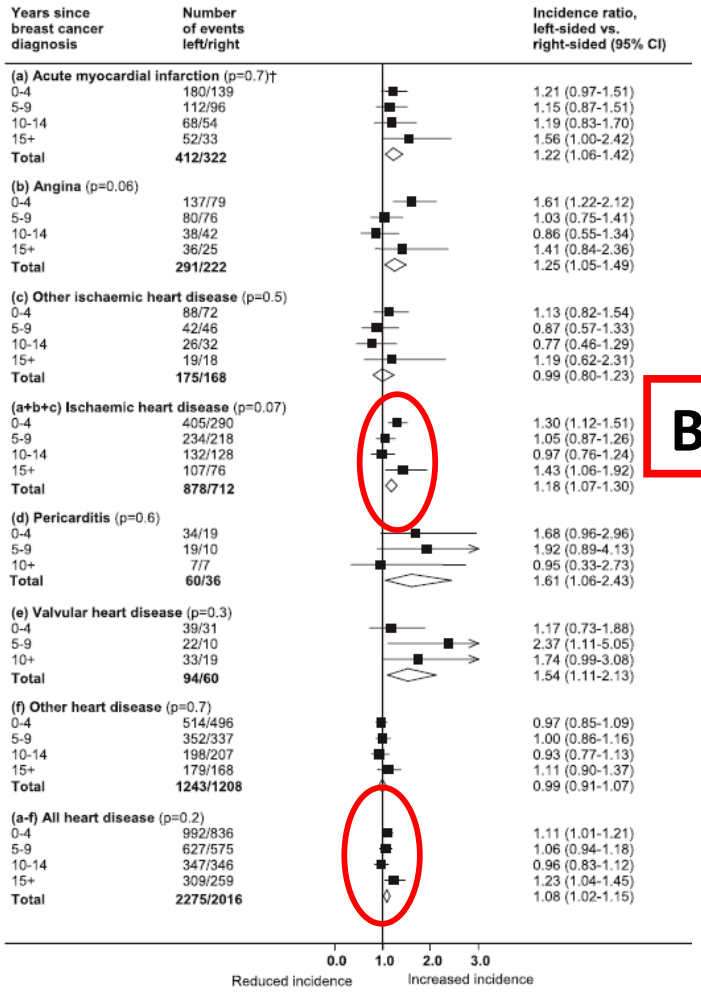
Big studies → big biases

Cardiac morbidity

Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden

Radiot and Oncol 100: 167 (2011)

Paul McGale [a], Sarah C. Darby [a,*], Per Hall [b], Jan Adolfsson [c], Nils-Olof Bengtsson [d], Anna M. Bennet [b], Tommy Fornander [e], Bruna Gigante [f], Maj-Britt Jensen [g], Richard Peto [a], Kazem Rahimi [h], Carolyn W. Taylor [a], Marianne Ewertz [i]



Big biases

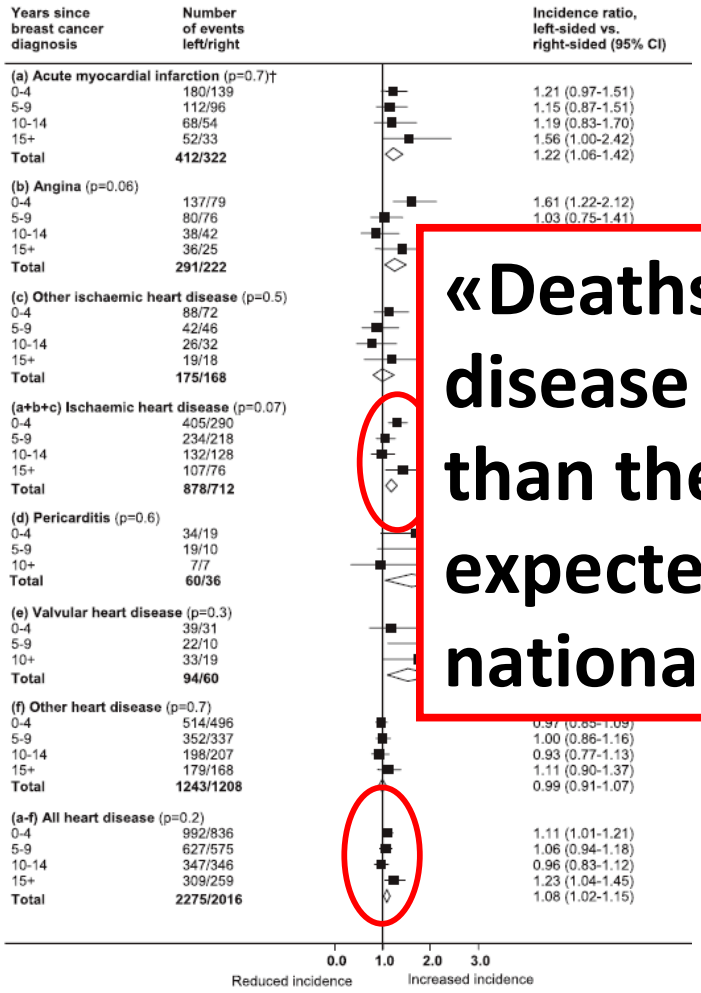
Characteristic	Percentage given radiotherapy		Number of women
	Left-sided breast cancer	Right-sided breast cancer	
Country			
Denmark	42	42	43,802
Sweden	58	58	28,332
Year of breast cancer diagnosis*			
1976–1989	43	44	27,898
1990–2006	51	51	44,236
Age at breast cancer diagnosis (years)			
<50	56	56	18,689
50–59	51	52	20,046
60–69	45	45	19,899
70–79	39	39	13,500
Breast-conserving surgery			
Yes	93	93	18,654
No/unknown†	33	33	53,480
Hormonal therapy			
Yes	56	56	22,427
No/unknown	44	45	49,707
Chemotherapy			
Yes	59	60	13,747
No/unknown	46	46	58,387
Ischaemic heart disease prior to breast cancer‡			
Yes	35	40	1766§
No/unknown	48	49	70,368
Other heart disease prior to breast cancer			
Yes	39	39	2413
No/unknown	48	49	69,721
Totals			
Percentage given radiotherapy	48	49	48
Number of women	37,269	34,865	72,134

Cardiac morbidity

Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden

Radiot and Oncol 100: 167 (2011)

Paul McGale [a], Sarah C. Darby [a,*], Per Hall [b], Jan Adolfsson [c], Nils-Olof Bengtsson [d], Anna M. Bennet [b], Tommy Fornander [e], Bruna Gigante [f], Maj-Britt Jensen [g], Richard Peto [a], Kazem Rahimi [h], Carolyn W. Taylor [a], Marianne Ewertz [i]



«Deaths from heart disease was lower than the number expected from national deaths rates»

Characteristic	Percentage given radiotherapy		Number of women
	Left-sided breast cancer	Right-sided breast cancer	
Country			
Denmark	42	42	43,802
Sweden	58	58	28,332
Year of breast cancer diagnosis*			
	43	44	27,898
	51	51	44,236
agnosis (years)			
	56	56	18,689
	51	52	20,046
	45	45	19,899
	39	39	13,500
ery			
	93	93	18,654
	33	33	53,480
	56	56	22,427
	44	45	49,707
	59	60	13,747
	46	46	58,387
prior to breast cancer‡			
Yes	35	40	1766§
No/unknown	48	49	70,368
Other heart disease prior to breast cancer			
Yes	39	39	2413
No/unknown	48	49	69,721
Totals			
Percentage given radiotherapy	48	49	48
Number of women	37,269	34,865	72,134

Editorial

Radiation-induced heart morbidity after adjuvant radiotherapy of early breast cancer – Is it still an issue?

Birgitte Offersen*, Inger Højris, Marie Overgaard

Department of Oncology, Aarhus University Hospital, Aarhus C, Denmark

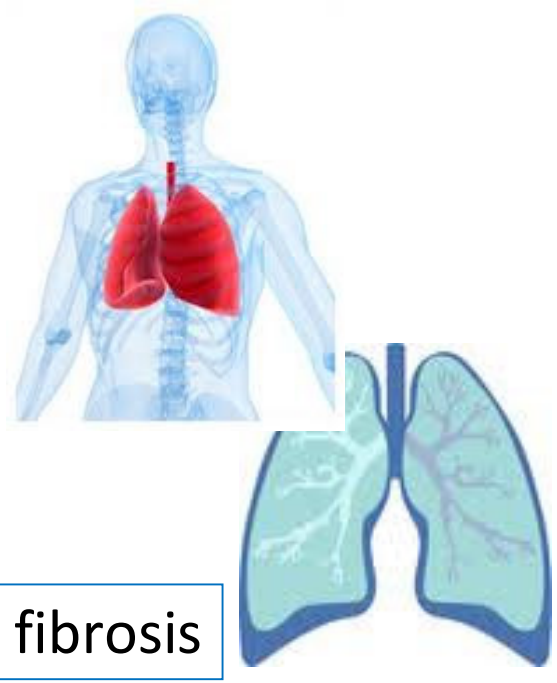
No! Yes!

Factors and unsolved issues of potential importance for the development of radiation-induced heart disease.

Aspect	Factors and unsolved issues of importance
Patient related	Age Long expected life-time Co-morbidities: connective tissue disease, hypertension, diabetes mellitus a.o. Systemic therapy may have negative influences on the heart: anthracyclines, trastuzumab, taxanes, tamoxifen, letrozole Risk that the systemic therapy potentiates the radiation effects on the heart Alcohol and tobacco Individual sensitivity to late heart morbidity Hereditary heart disease
Planning related	Irradiated volume of the heart Are some structures of the heart more sensitive to RT than others? Is the heart always a serial organ? Total dose and fractionation, boost Patient position during radiotherapy (prone/supine) Presence of hot spots in the heart
Technique related	Relevant organ at risk definition (what is relevant to delineate: heart, pericardium, some or all coronary vessels, valves). How to delineate this? What to report? Maximum or mean, V5, V10, V20? Inaccuracy in reporting doses due to different TPS and daily set up variation
Endpoint related	What heart morbidity is it relevant to look for? Is it possible to distinguish between radiation-induced heart disease and other far more frequent heart morbidities? How to measure the morbidity? Is it relevant to look for sub-clinical heart disease? For how long should the patient be evaluated, is it lifelong?
Ethical related	Is it acceptable to induce a fear of heart disease of around 1% absolute increased risk in a cancer patient? It is now technically feasible to (almost) avoid dose to the heart, so is a non-gated therapy for left-sided breast cancer no longer acceptable?
Society related	Is it cost-effective to set up screening programs to find those patients who may develop late radiation induced heart disease?

Radiot and Oncol 100: 157 (2011)

Lung



Early → pneumonitis

Late → fibrosis

QUANTEC MODEL: lung

Clinical aspects

- **Radiation clinical pneumonitis (RP) in 1-5 % of patients irradiated for breast**
- **endpoints: symptoms; radiologic alterations; pulmonary function**

Marks et al IJROBP 76(3) S70-76 (2010)

Not only QUANTEC: lung

PULMONARY CHANGES AFTER RADIOTHERAPY FOR CONSERVATIVE TREATMENT OF BREAST CANCER: A PROSPECTIVE STUDY

Marco Krengli, M.D.,* Mariano Sacco, M.D.,† Gianfranco Loi, Ph.D.,‡ Laura Masini, M.D.,* Daniela Ferrante, M.D.,§ Giuseppina Gambaro, M.D.,* Marco Ronco, M.D.,¶ Corrado Magnani, M.D.,§ and Alessandro Carriero, M.D.†

Grade	Before RT	3 mo after RT	9 mo after RT
0	41 (100)	9 (22.0)	9 (22.0)
1	0 (0)	19 (46.3)	24 (58.5)
2	0 (0)	10 (24.4)	8 (19.5)
3	0 (0)	3 (7.3)	0 (0)

88% of the case have G1-3 radiological evidence of damage → 4.9% had symptoms of G1 RP

Table 3. Mean lung volume receiving >25 Gy and corresponding grade of lung changes scored using classification of Nishioka *et al.* (18) at 3 and 9 months

	3-mo Assessment		9-mo Assessment	
Grade	Lung volume*	Proportion of lung volume	Lung volume*	Proportion of lung volume
0	67.8 (39.2)	0.05 (0.02)	70.4 (33.5)	0.05 (0.02)
1	86.0 (44.8)	0.07 (0.03)	92.6 (48.3)	0.07 (0.03)
2	131.9 (38.7)	0.10 (0.03)	147.5 (38.1)	0.11 (0.03)
3	157.6 (50.5)	0.10 (0.01)	—	—

Krengli et al IJROBP 70(5):1460 (2008)

QUANTEC MODEL: lung

Clinical aspects

- **Radiation clinical pneumonitis (RP) in 1-5 % of patients irradiated for breast**
- **endpoints: symptoms; radiologic alterations; pulmonary function**

Data about factors affecting the risk and about models used to predict the damage

- **NTCP: mean lung dose (MLD) model →**

…a variety of dose levels are predictive of RP suggests that there is no DOSE THRESHOLD below which there is no risk

- **"acceptable" risk level varies with the clinical scenario**

Marks et al IJROBP 76(3) S70-76 (2010)

QUANTEC MODEL: lung

Clinical aspects

- **Radiation clinical pneumonitis (RP) in 1-5 % of patients irradiated for breast**
- **endpoints: symptoms; radiologic alterations; pulmonary function**

Data about factors affecting the risk and about models used to predict the damage

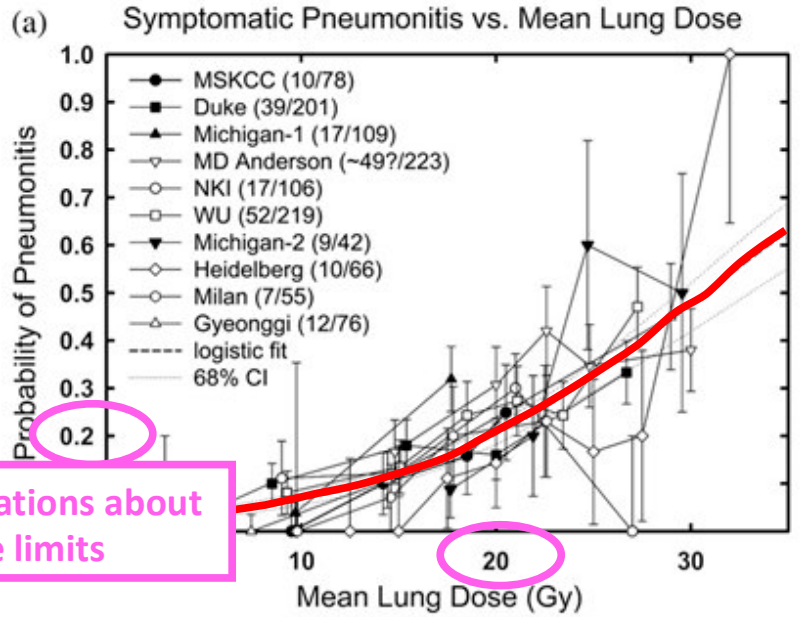
Recommendations about dose/volume limits

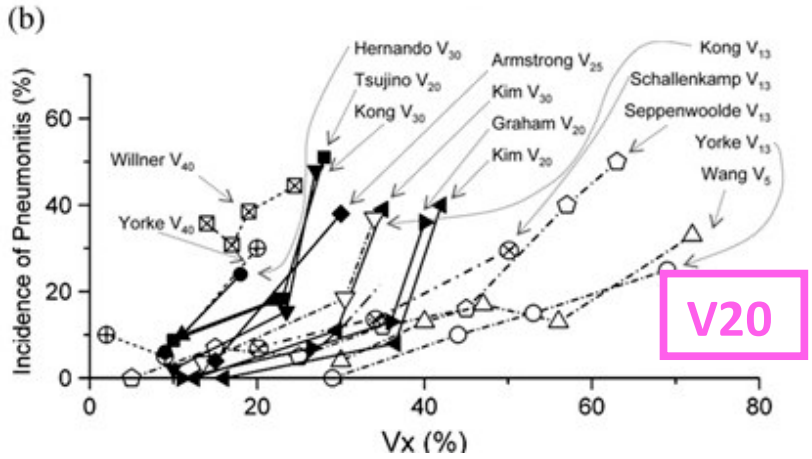
- **NTCP: mean lung dose (MLD) model →**

…a variety of dose levels are predictive of RP suggests that there is no DOSE THRESHOLD below which there is no risk

- **"acceptable" risk level varies with the clinical scenario**

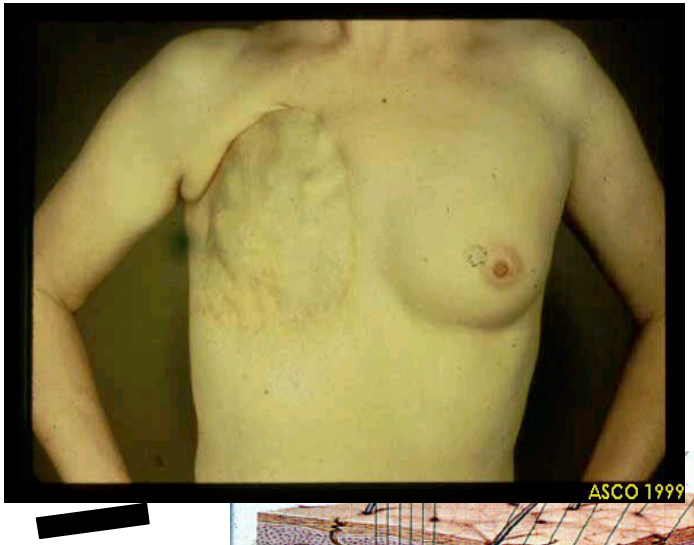
Data from literature



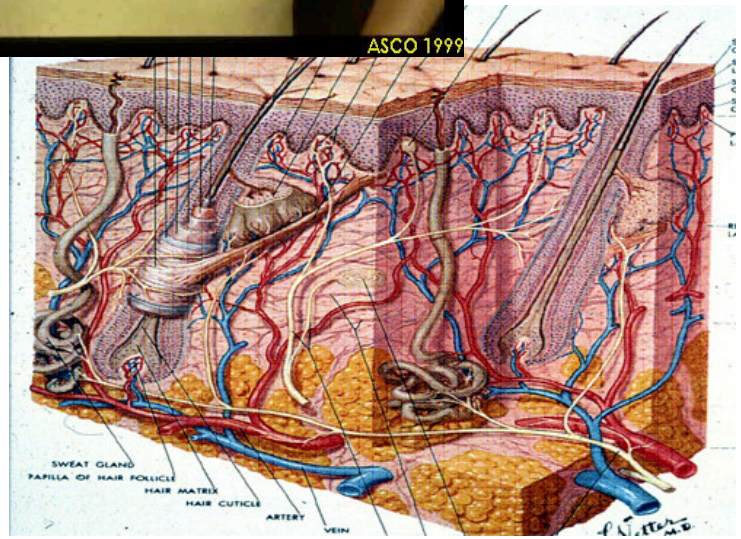


Marks et al IJROBP 76(3) S70-76 (2010)

Skin – Soft tissues



Early → dryness, epilation, pigmentation changes, and erythema



Sub-acute → Dry desquamation

Late →atrophy and fibrosis; pigmentation changes; telangiectasias

QUANTEC MODEL: skin→ does not exist

- It is a problem ↔ cosmetic outcome ↔ - discomfort
  - limit daily activities
  - breaks from treatm.

Factors related to skin toxicity

- factors different from RT as age, smoking, diabetes, others intrinsic factors
- total dose: in excess to 50 Gy to whole breast
- dose per fraction: not definitive results
- dose inhomogeneity → "double trouble" (hot spots created within inhomogeneous dose distribution ↑ total dose and ↑ dose per fraction)
- systemic treatment

Coles et al Clinical Oncol 17:16 (2005)

QUANTEC MODEL: skin→ does not exist

yes

- **It is still a problem? ↔ cosmetic outcome ↔ - discomfort**

ily activities

rom treatm.

« Previous

International Journal of Radiation Oncology * Biology * Physics
Volume 81, Issue 2 , Pages 397-402, 1 October 2011

Next »

Comparison of Provider-Assessed and Patient-Reported Outcome Measures of Acute Skin Toxicity During a Phase III Trial of Mometasone Cream Versus Placebo During Breast Radiotherapy: The North Central Cancer Treatment Group (N06C4)

Michelle A. Neben-Wittich, M.D., Pamela J. Atherton, M.S., David J. Schwartz, M.D., Jeff A. Sloan, Ph.D., Patricia C. Griffin, M.D., Richard L. Deming, M.D., Jon C. Anders, M.D., Charles L. Loprinzi, M.D., Kelli N. Burger, B.S., James A. Martenson, M.D., Robert C. Miller, M.D.

col 17(5): 22 (2010)

toxicity in breast cancer

Miao-Fen Chen[1,2*], Wen-Cheng Chen[1,2], Chia-Hsuan La

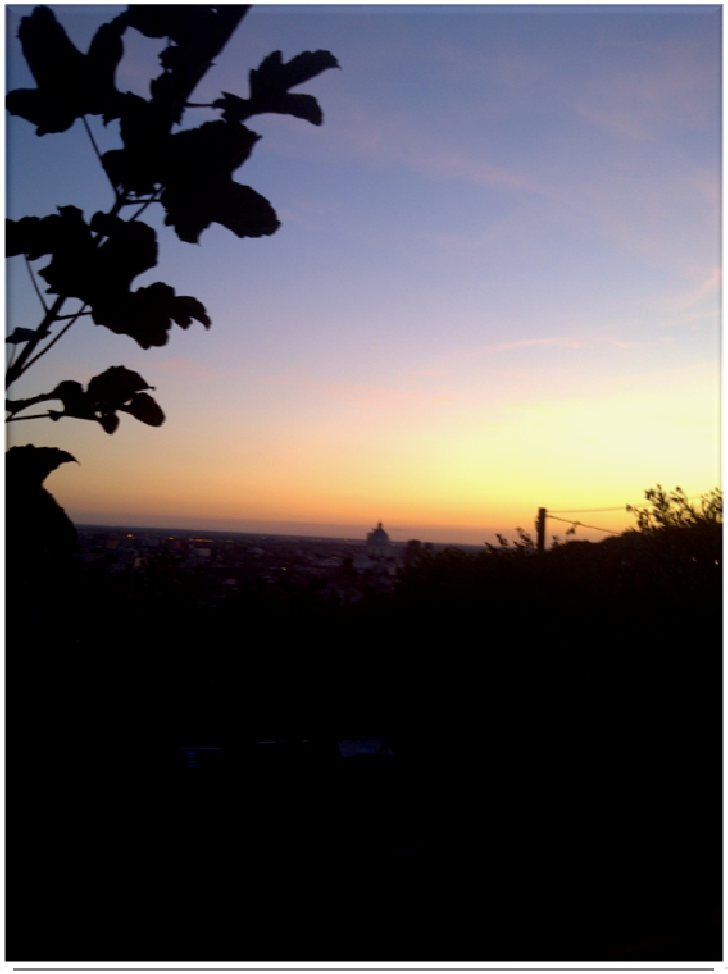
COLOGY

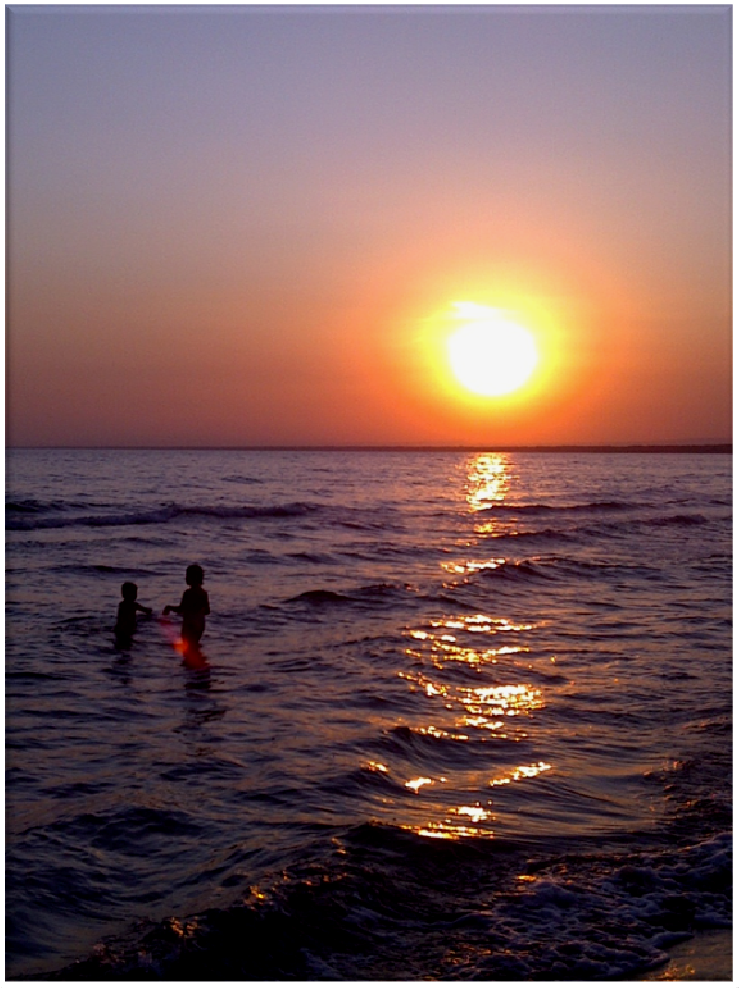
herapy

apy do

not increase radiation-induced dermatitis in breast cancer patients

T. Hijal MD, A.A. Al Hamad MD,† T. Niazi MD,† K. Sultanem MD,† B. Bahoric MD,† T. Vuong MD,† and T. Muanza MD†*





An accurate toxicity evaluation is mandatory :

- To *correlate* and *confirm (or not)* the data derived from theoretical mathematical models (e.g., α/β ratio) with adequate clinical data

- To *collect data* to guide therapeutic decisions

- **To *compare* the effectiveness and toxicities of the different treatment options**

Heart

QUANTEC

Lung

9. FUTURE TOXICITY STUDIES

Improved toxicity prediction requires prospective clinical trials based on 3D dosimetric data and careful long-term follow-up of patients who have received potentially cardiotoxic chemotherapy and RT. Prospective cardiac mortality studies are unlikely to be numerous. Hopefully, the few existing dose–volume predictors for cardiac mortality will be modified by new retrospective analyses based on larger data

a)

b)

data are lacking.

c) Future studies should incorporate baseline cardiovascular risk factors, such as the Framingham or Reynolds score (33–35). This will allow consideration of potential interactive effects between RT and traditional cardiac risk factors.
d) Additional work is needed to understand the impact of hypofractionated radiation regimens on the heart.
e) A deeper understanding of the global physiological effects of thoracic RT is needed (*e.g.*, interactions between the heart and lung irradiation, as suggested in some animal studies) (63).

9. FUTURE TOXICITY STUDIES

Progress regarding the predictors of RT-induced lung injury requires further understanding of the followin

Endpoint interaction

The study of RT-induced lung injury is confoun

RT was related to the volume of lung and heart (38–40).

Impact of an in situ lung cancer on the risk of radiation-induced lung injury

The data for whole-lung radiation is derived essentially from patients without primary lung cancers (e.g., elective

combined with the acute toxicities of amifostine (nausea/vomiting, hypotension, infection, and rash), have dissuaded many from using it in routine practice. One small randomized study demonstrated a protective effect of pentoxifylline, but pentoxifylline is not currently used in routine clinical practice (45).

Biomarkers

Additional work is needed to assess the predictive ability offered by biomarkers (see Bentzen *et al.* in this issue), such as transforming growth factor β (measured before and/or during RT) (46).

Key words:

- ✓ prospective clinical trials
- ✓ clear identification of end-point
- ✓ correlation of dosimetric informations with the clinic
- ✓ correlation of end-point – dosimetric information – clinical informations – biological informations