RAdiotherapy RElated Skin Toxicity:

Mepitel® Film vs. Standard Care in Patients with locally advanced Head-and-Neck Cancer

Trial name: RAREST-01

A multinational, randomized, active-controlled, parallel-group, multicenter trial

Sponsor:

University Hospital Schleswig-Holstein (UKSH), Campus Lübeck

Coordinating Investigator:

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Department of Radiation Oncology
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Confidentiality statement

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It has been confirmed that the protocol, the case report forms and appendices contain all information and regulations necessary for the implementation of the clinical trial, and that the trial will be conducted and documented in line with this protocol, abiding by the legal regulations and agreements described therein.

Sponsor of Study

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Represented by Prof. Dr. med. Dirk Rades
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1. Synopsis

1.1. English

Trial title	RAdiotherapy RElated Skin Toxicity: Mepitel® Film vs. Standard Care in Patients with locally advanced Head-and-Neck Cancer
Trial designation	RAREST-01
Sponsor	University Hospital Schleswig-Holstein (UKSH), Campus Lübeck
Trial manager	Prof. Dr. Dirk Rades Department of Radiation Oncology University of Lübeck, Germany
Trial start	März 2017
Recruitment period	24 months
Type of protocol	Multinational, randomized, active-controlled, parallel-group, multi-center trial
Indication	Radiotherapy or Radiochemotherapy of Head-and-Neck Cancer
Objectives	The primary goal of this randomized trial is to demonstrate that Mepitel® Film is superior to Standard Care with respect to prevention of grade ≥2 radiation dermatitis in patients receiving radio(chemo)therapy for locally advanced SCCHN.
Primary endpoint	Rate of patients experiencing grade ≥2 radiation dermatitis (CTCAE v4.03) until 50 Gy of radiotherapy
Secondary aims	1. Time to grade 2 radiation dermatitis until 50 Gy of radiotherapy 2. Rate of patients experiencing grade ≥2 radiation dermatitis during radio(chemo)therapy 3. Rate of patients experiencing grade ≥3 skin toxicity during radio(chemo)therapy 4. Adverse Events 5. Quality of life: Evaluation prior to radiotherapy, at the end of radiotherapy weeks 3 + 5, and at 3 weeks following radiotherapy 6. Pain (radiation fields): Evaluation prior to radiotherapy, during RT daily, at the end of radiotherapy weeks 3 + 5, and at 3 weeks following radiotherapy 7. Grade ≥2 dermatitis at 60 Gy and at the end of radiotherapy (EOT)
Treatment	Patients will be randomized in a ratio of 1:1 to arm A and arm B: **Arm A:** Treatment with Mepitel® Film, starting at the beginning of

	radiotherapy. **Arm B:** Treatment with Standard Care, starting at the beginning of radiotheraphy. In case of grade 2 moist desquamation or any grade 3 radiation dermatitis, patients will be treated with local antisepctic agents plus fatty cream and absorbing silicon bandage. Follow-up: until 3 weeks following radiotherapy
Number of patients	168 patients (84 patients per arm)
Inclusion criteria	1. Histologically proven locally advanced squamous cell carcinoma of the head-and-neck (SCCHN) 2. Conventionally fractionated (5 x 2 Gy per week) definitive or adjuvant radio(chemo)therapy 3. Age ≥18 years 4. Written informed consent 5. Capacity of the patient to contract
Exclusion criteria	1. N3 stage (lymph nodes >6 cm) 2. Distant metastases (M1) 3. Pregnancy, Lactation 4. Treatment with EGFR-antibodies (either given or planned) 5. Expected non-compliance
Statistics / Sample size calculation	With 80 patients qualifiying for Full Analysis Set in each group, a two-sided chi-square test with a 5% two-sided significance level will have 80% power to yield statistical significance if the rate of grade ≥2 radiation dermatitis in patients receiving standard care for skin toxicity is 85% compared to 65% in patients treated with Mepitel® Film. Taking into account that 5% of patients will not qualify for Full Analysis Set, a total of 168 patients should be randomized.The confirmatory evaluation will be performed within the Full Analysis Set, which comprises all randomized patients who have started either therapy with arm A or with arm B. Cochran-Mantel-Haenszel Chi-square tests will be used for non-parametric assessment of the overall treatment effect, while adjusting for the effects of the stratification variables. For sensitity analysis, a logistic regression model for grade ≥2 radiation dermatitis will be applied including the parameters used for stratification. In addition, a model including also additional patient characteristics will be fitted. To evaluate the tolerance and acceptance of the Mepitel® Film treatment after one third of the study an interim analysis will be conducted after inclusion of 57 patients. The recruitment will be put on hold until the 57 patients have completed the study. Depending on the proportion of patients who did not tolerate or accept Mepitel® Film, the study will be continued or terminated. Furthermore, the skin toxicity between both treatment groups will be compared.
End of study	April 2019 (last patient out).

1.2. German

Studientitel	**Strahlentherapie-bedingte Hautreaktionen: Mepitel® Film im Vergleich zur Standardbehandlung bei Patienten mit lokal fortgeschrittenem Kopf-Hals-Tumor**
Studienkürzel	RAREST-01
Sponsor	Universitätsklinikum Schleswig-Holstein (UKSH), Campus Lübeck
Studienleiter	Prof. Dr. Dirk Rades Klinik für Strahlentherapie Universität zu Lübeck
Start der Studie	März 2017
Rekrutierungs-zeitraum	24 Monate
Studiendesign	Randomisiert, aktiv-kontrolliert, parallel, multizentrisch
Indikation	Strahlentherapie oder Radiochemotherapie bei einem Kopf-Hals-Tumor
Zielsetzung	Die primäre Fragestellung dieser randomisierten Studie ist der Nachweis, dass Mepitel® Film der Standardbehandlung hinsichtlich der Vermeidung einer Strahlendermatitis Grad ≥2 bei Patienten, die eine Radio(chemo)therapie bei einem lokal fortgeschrittenen SCCHN erhalten, überlegen ist.
Primärer Endpunkt	Rate der Patienten, bei denen während der Strahlentherapie bis 50 Gy eine Dermatitis Grad ≥2 (CTCAE v4.03) auftritt
Sekundäre Endpunkte	1. Zeit bis zum Auftreten einer Strahlendermatitis Grad 2 bei Bestrahlung bis 50 Gy 2. Rate der Patienten, bei denen während der Radio(chemo)therapie eine Strahlendermatitis ≥ Grad 2 auftritt 3. Rate der Patient, bei denen während der Radio(chemo)therpie eine Strahlendermatitis ≥ Grad 3 auftritt 4. Nebenwirkungen 5. Lebensqualität: Bewertung vor Bestrahlung, zum Ende der Bestrahlungswochen 3 und 5 sowie 3 Wochen nach Bestrahlung 6. Schmerz (Strahlenfelder): Bewertung vor Bestrahlung, täglich während der Strahlentherapie, am Ende der Bestrahlungswochen 3 und 5 sowie 3 Wochen nach Bestrahlung 7. Grad ≥2 Dermatitis bei 60 Gy und am Ende der Strahlentherapie (EOT)
Patientenanzahl	168 Patienten (84 Patienten pro Arm)
Behandlung	Patienten werden 1:1 in Arm A oder Arm B randomisiert: **Arm A:** Behandlung mit Mepitel® Film startet mit Beginn der Strahlentherapie. **Arm B:** Standardbehandlung startet mit Beginn der Strahlentherapie. Bei feuchten Epitheliolysen Grad 2 oder jeglicher Strahlendermatitis Grad 3 werden die Patienten lokal mit antiseptischen Mitteln plus einer

	fetthaltigen Creme und Silikonverband behandelt. Follow-up: bis 3 Wochen nach Strahlentherapie
Einschlusskriterien	1. Histologisch gesichertes lokal fortgeschrittenes Plattenepithelkarzinom der Kopf-Hals-Region (SCCHN) 2. Konventionell fraktionierte (5 x 2 Gy pro Woche) definitive oder adjuvante Radio(chemo)therapie 3. Alter ≥18 Jahre 4. Schriftliche Einverständniserklärung
Ausschlusskriterien	1. N3 Stadium (Lymphknoten >6 cm) 2. Fernmetastasen (M1) 3. Schwangerschaft, Stillzeit 4. Behandlung mit EGFR-Antikörpern (auch geplant) 5. Zu erwartende Non-Compliance
Statistik / Fallzahl-kalkulation	Wenn 80 Patienten pro Gruppe für das Full-Analysis-Set in Frage kommen, wird der zweiseitige Chi-Quadrat-Text bei einem Signifikanzniveau von 5% eine Power von 80% aufweisen. Wenn die Rate an Grad ≥2 Strahlendermatitiden bei Patienten/innen im Standard Arm (B) 85% und bei Patienten/innen im experimentellen Arm (A) 65% beträgt, wird die Überlegenheit als signifikant angesehen. Wenn man davon ausgeht, dass sich 5% der Patienten nicht für das Full-Analysis-Set qualifizieren, müssen 168 Patienten randomisiert werden.Der Wirksamkeitsnachweis wird mit dem Full-Analysis-Set durchgeführt, welches alle randomisierten Patienten beinhaltet, die ihre Behandlung entweder im Arm A oder Arm B begonnen haben. Der Cochran-Mantel-Haenszel Chi-Quadrat-Test wird zum nicht-parametrischen Nachweis des Behandlungseffektes verwendet. Adjustiert wird nach den Effekten der Stratifizierungsvariablen. Für die Sensitivitätsanalyse wird ein logistisches Regressionsmodell für die Strahlendermatitis Grad ≥2 angewendet, welches die Stratifizierungparameter berücksichtigt. Zusätzliche wird ein Modell verwendet, welches auch an zusätzliche Charakteristika der Patienten angepasst ist. Um die Toleranz und Akzeptanz des Mepitel® Film Produktes nach einem Drittel der Study zu evaluieren wird nach der Behandlung von 57 Patienten eine Interimsanalyse durchgeführt. Die Rekrutierung wird unterbrochen, nachdem die 57 Patienten die Studie beendet haben. Je nach dem Anteil der Patienten, die Mepitel® Film nicht toleriert oder akzeptiert haben, wird die Studie fortgesetzt oder beendet. Außerdem wird die Hauttoxizität zwischen den beiden Behandlungsgruppen verglichen.
Studienende	April 2019 (last patient out)

2. Flow Chart

	Prior to radiotherapy	During Treatment (weeks 1, 2, 4)	During Treatment (weeks 3 + 5)	Following Treatment (Last day of treatment [EOT], weeks 1 + 3)
Informed Consent	X			
Medical History	X			
Demographic Data	X			
Concomitant Medication	X			
Patient Characteristics	X			
Randomization	X			
Physical Examination	X	X	X	X
Adverse Events, Serious Adverse Events	X	X	X	X
Skin status defined as radiation dermatitis acording to CTCAE v4.03		X (daily)	X (daily)	X (daily)
Quality of Life	X		X	X (week 3)
Other Toxicities		X	X	X
Pain score	X	X (daily)	X (daily)	X (EOT, week 3)
Radio(chemo)therapy (administered as planned)		X	X	

3. Background and Rationale

Locally advanced squamous head-and-neck cancer is a serious malignant disease. In about 90% of head-and-neck cancers, the histology is squamous cell carcinoma (SCCHN). The vast majority of patient with locally advanced SCCHN receive radiotherapy, either as a part of a definitive treatment approach, or as an adjuvant treatment following surgery. If radiotherapy is administered as definitive treatment, it is usually combined with concurrent cisplatin-based chemotherapy [1]. In an adjuvant situation, chemotherapy will be added to radiotherapy in case of risk factors, namely microscopically or macroscopically incomplete resection or in case of extra-capsular spread of lymph nodes metastases.

Radiotherapy of locally advanced SCCHN may be associated with severe acute toxicities including skin reaction such as erythema or desquamation. Skin toxicity is enhanced if concurrent chemotherapy is administered. If the skin toxicity becomes severe (grade ≥3 according to the Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.03), it may lead to a reduction of the planned chemotherapy dose and to interruptions of radiotherapy. Interruptions of radiotherapy have to be reported to be associated with poorer treatment outcomes in patients with SCCHN [2,3].

In order to successfully avoid grade ≥3 skin toxicity, it appears mandatory to avoid or at least postpone the development of grade 2 skin toxicity. In previous studies of patients receiving radiotherapy or radio(chemo)therapy for locally advanced head-and-neck cancer, rates of grade ≥2 skin toxicity ranging between 86% and 92% have been reported, although the standard procedures of skin care and protection had been applied [1, 4, 5]. These figures demonstrate that the results of standard care need to be improved.

Three years ago, the results of a systematic inpatient controlled clinical trial were published that had investigated the use of an absorbent, self-adhesive dressing (Mepilex® Lite) for skin protection in patients irradiated for breast cancer [6]. According to this study the dressings were able to significantly reduce the radiation-related skin erythema. Similar dressings (Mepilex® Border Sacrum and Mepilex® Heel dressings) have been demonstrated in a randomized trial to be effective also in the prevention of sacral and heel pressure ulcers in trauma and critically ill patients [7]. In another randomized trial a silver-containing soft silicone foam dressing (Mepilex® Ag dressing) was as effective in the treatment of partial-thickness thermal burns when compared to the standard care (silver sulfadiazine) [8]. In addition, the group of patients treated with the Mepilex® Ag dressing demonstrated decreased pain and lower costs associated with treatment. More recently, a new dressing (Mepitel® Film) has been developed, which is thinner, softer and more comfortable than previous dressings.

The rationale for the present study is to investigate a new option of skin protection in order to reduce the rate of grade ≥2 skin toxicity in patients receiving radiotherapy alone or radiochemotherapy for locally advanced SCCHN.

4. Objectives

The primary goal of this randomized trial is to demonstrate that Mepitel® Film is superior to Standard Care with respect to prevent grade ≥2 radiation dermatitis in patients receiving radio(chemo)therapy up to 50 Gy for locally advanced SCCHN.

5. Endpoints

5.1. Primary endpoint

The primary aim of this randomized multinational multicenter trial is to investigate the rate of patients experiencing grade ≥2 radiation dermatitis (CTCAE v4.03) until 50 Gy of radiotherapy.

Evaluation until 50 Gy of radiotherapy has been selected as the primary endpoint, since up to 50 Gy, the irradiated volume includes the primary tumor and the bilateral cervical and supraclavicular lymph nodes, and, therefore, is almost identical in all patients. After 50 Gy, the irradiated volume is much more individual, depending on location and size of the primary tumor, involvement of lymph nodes, and the treatment approach (definitive vs. adjuvant).

5.2. Criteria for secondary aims

In addition, the following endpoints will be evaluated:

1. Time to grade 2 radiation dermatitis until 50 Gy of radiotherapy
2. Rate of patients experiencing grade ≥2 radiation dermatitis during radio(chemo)therapy
3. Rate of patients experiencing grade ≥3 skin toxicity during radio(chemo)therapy
4. Adverse Events
5. Quality of life: Evaluation prior to radiotherapy, at the end of radiotherapy weeks 3 + 5, and at 3 weeks following radiotherapy
6. Pain (radiation fields): Evaluation prior to radiotherapy, during radiotherapy daily at the end of radiotherapy weeks 3 + 5, and at 3 weeks following radiotherapy
7. Rate of patients experiencing a grade ≥2 dermatitis at 60 Gy and at the end of radiotherapy (EOT)

6. Trial design

6.1 General trial design and duration

This is a randomized, active-controlled, parallel-group trial, which will compare the following treatments of radiation related skin toxicity in patients with head-and-neck cancer:

Mepitel® Film (Arm A) vs. Standard Care (Arm B).

A total of approximately 4 contributing centers are planned to participate, who aim to include an average of 21 patients per year. The recruitment of all 168 patients should be completed within 24 months. The follow-up period will be 3 weeks. This equals a total running time for the trial of 25 months.

Stratification will be done using the following prognostic factors:

1. Tumor site: oropharynx/oral cavity vs. hypopharynx/larynx
2. Treatment approach: radiochemotherapy vs. radiotherapy alone
3. Participating site

In case of uneven distribution to stratification groups, which may result in very small groups the strata might be connected for analysis. The decision to merge strata for the analysis will be made before data base lock and before the final analysis of the data.

To evaluate the tolerance and acceptance of the Mepitel® Film treatment after one third of the study an interim analysis will be conducted after inclusion of 57 patients. The recruitment will be put on hold until the 57 patients have completed the study. Depending on the proportion of patients who did not tolerate or accept Mepitel® Film, the study will be continued or discontinued. Furthermore, the skin toxicity between both treatment groups will be compared.

6.2 Patient selection

This trial will be performed in patients receiving definitive or adjuvant radio(chemo)therapy for locally advanced squamous cell carcinoma of the head-and-neck (SCCHN).

6.2.1 General prerequisites

Patients must be adequately informed about their diagnosis and about the nature, significance and scope of the trial. Patients may only be included after completing the pre-therapy clarification and on fulfillment of all inclusion criteria and on non-fulfillment of all exclusion criteria.

6.2.2 Inclusion and exclusion criteria

Inclusion criteria	1. Histologically proven locally advanced squamous cell carcinoma of the head-and-neck (SCCHN) 2. Conventionally fractionated (5 x 2 Gy per week) definitive or adjuvant radio(chemo)therapy 3. Age ≥18 years 4. Written informed consent 5. Capacity of the patient to contract
Exclusion criteria	1. N3 stage (lymph nodes >6 cm) 2. Distant metastases (M1) 3. Pregnancy, Lactation 4. Treatment with EGFR-antibodies (either given or planned) 5. Expected non-compliance

6.2.3 Termination criteria for individual patients

The patient may terminate participation in the trial at any time and without giving any reasons. If the patient agrees, follow up will be performed as planned to receive data even in case of termination of participation in the study.

Otherwise, the reasons for terminating participation in the trial are the same as those for individually breaking off treatment with radiotherapy. In the cases, follow up will be completed as planned.

- Serious adverse event, which necessitates termination of treatment
- Unacceptable toxicities
- Pregnancy

Date and reason for termination of treatment must be documented.

6.2.4 Definition of the end of the trial

The trial ends after a follow-up for at least 3 weeks following radio(chemo)therapy.

6.2.5 Stopping Rules

Individual patients

Randomized patients have the right to discontinue participation at any time without penalty or loss of benefits to which the subject would otherwise be entitled.

Study site suspension or early termination

The coordinating principal investigator and ethics committee have the right to suspend or terminate a participating site for any of the following possible reasons: Noncompliance to obtain patient informed consent; unsatisfactory rate of patient enrollment or compliance to eligibility criteria; repeated noncompliance with the investigational plan; inaccurate, incomplete, and/or untimely submission of data.

To evaluate the tolerance and acceptance of the Mepitel® Film treatment after one third of the study an interim analysis will be conducted after inclusion of 57 patients. The recruitment will be put on hold until the 57 patients have completed the study. Depending on the proportion of patients who did not tolerate or accept Mepitel® Film, the study will be continued or discontinued. Furthermore, the skin toxicity between both treatment groups will be compared.

The trial may be stopped prematurely by the principal investigator in case of safety reasons that do not appear to be reasonably justified. In case of a prematurely termination of the trial, the patient and the ethics committee will be informed promptly. An appropriate further therapy and follow-up is assured for the patient.

6.3 Timeline

First Patient In March 2017

Last Patient In February 2019

Last Patient Out April 2019

End of Study August 2019

7 Treatment

7.1 Patient registration and randomization

The patients will be assigned two code numbers: the number of the contributing center plus a patient ID number, continuously ascending, starting with 001.

After registration, patients will be randomized in a 1:1 ratio to receive either Mepitel® Film (Arm A) or Standard Care (Arm B) for treatment of radiation related skin toxicity.

A stratified blockrandomization will be performed. The stratification (approximately 4 center, 2 treatment approaches, 2 tumor sites) will be conducted as described in section 6.1. Further details with regard to the randomization will be described in a separate document referred to as ”Festlegen der Parameter für die Randomisierung”.

The randomization will be performed centrally at the ‘Zentrum für Klinische Studien’ (ZKS) at the University of Lübeck, Germany via Fax: +49-(0)451-500-50614. The randomization is possible from Monday to Thursday 8.00 a.m. to 4.00 p.m., Friday 8.00 a.m. to 2.00 p.m. (exclusion: no randomization will be conducted between 24th of December and 1st of January). The proceeding is based on standard operating procedures (SOPs) of the ZKS. The fax document has to be completed and finally be signed and dated by the investigator. Once the randomization is allocated to the patient it cannot be changed.

7.2 Treatment

7.2.1 Radiotherapy

Radiotherapy is administered using conventional fractionation (5 x 2.0 Gy per week).

In all patients, the initial target volume includes the region of the primary tumor plus bilateral cervical and supraclavicular lymph nodes up to 50 Gy.

Patients treated with adjuvant radiotherapy following complete resection of the primary tumor and the involved lymph nodes (R0-resection) receive a radiation boost of 10 Gy (5 x 2.0 Gy per week) to the regions of the primary tumor and the involved lymph nodes.

In case of a microscopically incomplete resection (R1-resection), the boost dose to the primary tumor region is 16 Gy.

In case of extra-capsular spread (ECS) of lymph nodes, the lymph nodes showing ECS receive an additional boost of 6 Gy (i.e. a cumulative boost dose of 16 Gy).

Patients receiving definitive radiotherapy, receive a boost of 10 Gy (5 x 2.0 Gy per week) to the primary tumor, the involved lymph nodes, and the lymph node levels adjacent to the involved lymph nodes. An additional boost of another 10 Gy (5 x 2.0 Gy per week) is administered to the primary tumor and the involved lymph nodes.

Treatment should be performed as either intensity-modulated radiotherapy (IMRT) or volumetric modulated arc theray (VMAT) radiotherapy.

The rate of patients experiencing grade ≥2 radiation dermatitis (CTCAE v4.03) until the fifth week of therapy (50 Gy) is in focus of this clinical study. In addition to this observation period another 2 weeks of radiotherapy (up to 70 Gy) might be performed. This further treatment will be conducted in accordance with common treatment guidelines. The treatment of the patients > 50 Gy will not be analyzed within this study. The occurrence of adverse events and serious adverse events will be documented for the complete duration of radiotherapy. The final dose of radiotherapy received by the patient has to be documented in the Case Report Form (CRF).

7.2.2. Concomitant Chemotherapy

In patients who receive definitive radiochemotherapy, concomitant chemotherapy with two courses of cisplatin (20 mg/m^2/d1-5 or 25 mg/m^2/d1-4), carboplatin (5xAUC 1.0 or 4xAUC 1.5) or mitomycin C (20 mg/m^2/d1) + 5-fluororuracil (1000 mg/m^2/d1-5) is administered. Cisplatin,carboplatin and mitomycin C/5-fluorouracil are among effective and usedas radiosensitizers in the treatment of head-and-neck cancer patients. In this trial commercially available cisplatin,carboplatin, mitomycin C and 5-fluorouracil are used. Cisplatin is considered the standerad regimen. Carboplatin will be used in case of mild impairment of kidney function, and mitomycin C/5-fluorouracil in case of moderately impaired kidney function. Cisplatin, carboplatin or mitomycin will be administered after saline hydration as intravenous bolus infusion. The saline hyper-hydration will be given according to the investigational centre's routine. All patients treated with cisplatin, carboplatin or mitomycin C/5-fluorouracil in addition to radiotherapy must receive adequate anti-emetic therapy prior to the administration. It is recommended that a 5HT3 antagonist (e.g. granisetrone) and dexamethasone 8 mg i.v. are administered prior to each cycle of treatment. 5-fluororuracil (1000 mg/m2/d1-5) will be adimistered as continuous infusion over 120 hours.

7.2.3. Possible side effects of radio(chemo)therapy

In addition to skin toxicity, radio(chemo)therapy may be associated with other side effects such as mucositis, taste disorders, xerostomia, nausea and vomiting, fatigue, renal dysfunction, and pancytopenia. In case of such a grade 3 toxicity according to CTCAE criteria, radio(chemo)therapy may be delayed for a maximum of 7 days without consequences. If it is delayed for longer than 7 days, the coordinating investigator of the clinical trial must be informed.

7.2.4. Arm A: Mepitel® Film

At the beginning of radiotherapy Mepitel® Film will be applied to the patient. The treatment will be continued until one week after the end of the treatment period or until a patient experiences grade ≥2 moist desquamation or grade ≥3 radiation dermatitis. In case of grade ≥2 moist desquamation or grade ≥3 radiation dermatitis, each day antiseptic agents will be administered for wound cleansing followed by administration of silicon or calcium alginate bandage. This treatment will be continued until moist desquamation radiation disappears and radiaton dermatitis improves to grade 2.

Mepitel® Film is an ultra thin, transparent, breathable soft silicone film dressing.

Product description

Mepitel® Film is a gentle, sterile, transparent, breathable film dressing consisting of polyurethane film coated with a Safetac® contact layer. The film dressing is supported with a paper frame for ease of application.

Safetac® Technology

Safetac® is a patented soft silicone adhesive technology that minimizes pain to patients and trauma to wounds. Safetac® technology is less painful because it

1. tacks gently to dry surfaces, like skin, but not to moist surfaces such as open wounds

2. moulds to the skin's pores, covering more skin surface and spreading peel forces on removal to prevent skin stripping

3. seals the wound margins, ensuring exudates do not spread to the surrounding skin and minimizing maceration

Mode of action

Mepitel® Film provides a flexible, transparent covering to protect the skin or wound from microbial contamination, fluid strike through and from other external contamination while conforming to surface irregularities and body contours.

Mepitel® Film maintains a moist environment even though the vapor permeability allows excess moisture to pass away from the skin.

Mepitel® Film provides instant tack adhesion that minimizes the requirement of extra pressure in order to fixate well. The product does not leave residues and the adhesion level does not increase over time.

Mepitel® Film is a protective layer that may reduce the shear and friction on the skin and may help to prevent skin breakdown.

Fixation tapes can be fixated on top of the Mepitel® Film product, the Mepitel® Film is then used as a protective Landing Zone™ for the fixation tape.

Mepitel® Film is skin-friendly, non-irritant and non-sensitizing. Mepitel® Film is waterproof.

Intended Use

Mepitel® Film is designed for the management for a wide range of superficial wounds such as pressure ulcers stage/grade I and II, superficial burns, superficial skin injuries and it may help to prevent skin breakdown. Mepitel® Film protects fragile and sensitive skin.

Mepitel® Film can also be used as a protective cover for open surgical wounds (e.g. abdomen), fixate primary dressing as a secondary dressing and be used in combination with gels and ointments.

Instructions for use:

1. Clean the application area in accordance with normal procedures.

Dry the skin/surrounding skin thoroughly.

Remove the protection film (printed side) and apply the adherent side to the wound and smooth Mepitel® Film in place, ensuring a good seal. Do not stretch. The shape of the product may not be optimal at difficult to dress areas.

Mepitel® Film can be repositioned as long as the paper frame is intact. Remove the paper frame.

For best result, Mepitel® Film should overlap the dry surrounding skin by at least 1-2 cm for the smaller sizes (sizes up to 10x12 cm) and 5 cm for the larger sizes in order to fixate the dressing securely.

The dressing can be removed without causing skin stripping and pain.

Frequency of change
Mepitel® Film may be left in place for several days depending on the condition of the skin or wound and the surrounding skin, or as indicated by accepted clinical practice.

Precautions
Do not use as primary fixation for IV, cannulae, ports, or other infusion and / or life sustaining devices.

Mepitel® Film is not a wound contact layer product and does not allow wound exudates to pass trough the dressing to a secondary layer.

If more than one product is used and they are overlapped, the vapor permeability goes down; this can lead to excess moisture not being allowed to pass away from the skin.
In case of signs of clinical infection, consult a health care professional for adequate infection treatment.

Do not reuse. If reused performance of the product may deteriorate, cross contamination may occur.

Do not use if inner package is damaged or opened prior to use. Do not re-sterilize.

7.2.5. Arm B: Standard Care of radio(chemo)therapy

At the beginning of radiotherapy standard skin care will be applied to the patient. This may vary at the participating centers. At the University of Lübeck, it includes two components, fatty cream with 2-5% urea (fatty cream alone, if patients do not tolerate urea) and mometasone furoate cream. The treatment will be continued until one week after the end of the treatment period or until a patient experiences grade ≥2 moist desquamation or grade ≥3 radiation dermatitis. In case of grade ≥2 moist desquamation or grade ≥3 radiation dermatitis, each day antiseptic agents will be administered for wound cleansing followed by administration of silicon or calcium alginate bandage. This treatment will be continued until moist desquamation radiation disappears and radiaton dermatitis improves to grade 2.

Cream

Fatty cream with 2-5% urea is applied to the irradiated skin 3-4 times daily.

Mometasone furoate cream

In addition to the fatty cream with 2-5% urea, mometasone furoate cream (solution 0.1%) is applied to the irradiated skin once daily.

Mometasone furoate cream is used in the treatment of inflammatory skin disorders. In terms of steroid strength, it is more potent than hydrocortisone, and less potent than dexamethasone. It reduces inflammation by causing several effects such as reversing the activation of inflammatory proteins, activating the secretion of anti-inflammatory proteins, stabilizing cell membranes, and decreasing the influx of inflammatory cells. The exact anti-inflammatory mechanism of action is unknown.

8. Safety management

8.1. Definitions

8.1.1. Adverse events

An adverse event is any event experienced by a patient or subject of a clinical trial, which does not necessarily have a causal relationship to treatment. An adverse event (AE) can therefore be any adverse or inadvertent occurrence (including notable laboratory findings), symptom or illness that occurs in the treatment period, no matter whether there is a causal relationship or not. Existing illnesses that deteriorate during the trial should be reported as adverse events. They may lead to serious adverse events if they fulfill the criteria below.

Events covered by the documentation for concomitant diseases, the skin status or the radiation related acute toxicity grade (CTCAE v4.03) Grade 1 do not have to be additionally documented as adverse events. If an additional concomitant disease appears after the start of the study an adverse event form has to be completed.

8.1.2 Unexpected adverse events

Unexpected adverse events are those whose type, frequency and degree of severity are not expected based on current knowledge.

8.1.3. Serious adverse events

Serious adverse events are those which fulfill one of the following criteria at any dose level:

- Lethal (resulting in death) event (Note: death is the result, not the event itself)
- Life-threatening event (Note: the term “life-threatening” refers to an event in which the patient was in danger of death at the time the event occurred but not to an event that may have resulted in death had it been more serious.)
- Patient had to be admitted to hospital or his/her hospital stay had to be extended as a result of the event
- Any event leading to permanent or significant disability.

- Birth defects or malformations
- Any medically significant event or any event necessitating surgery in order to prevent one of the abovementioned concomitant illnesses

Hospitalization should be defined as such that the hospitalization was necessary in order to treat the adverse event. Hospital stays as part of the treatment outlined in the protocol or as a result of a planned, elective operation are not classed as serious adverse events. Likewise, an elective hospitalization to facilitate the trial process does not count as a serious adverse event.

8.2 Assessment and documentation of adverse events

The severity of adverse events should be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. If an adverse event occurs which is not described in the CTCAE version 4.03, the five-point scale below will be used.

scale: 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening and 5 = fatal.

The following scale should be used to describe the likelihood that the event was caused by the trial treatment:

1 = certain / definite;

2 = probable;

3 = possible;

4 = unlikely;

5 = not related;

6 = not assessable.

8.3 Reporting of serious adverse events and unexpected adverse events

Serious adverse events and unexpected adverse events must be reported within 24 hours after their detection/onset by fax to the address below:

Prof. Dr. Dirk Rades
Klinik für Strahlentherapie, Universität zu Lübeck
Ratzeburger Allee 160; 23538 Lübeck, Germany
Tel.: +49-(0)451-500-45400 **Fax: +49-(0)451-500-45404**
Email: rades.dirk@gmx.net and dirk.rades@uksh.de

9. Examinations

9.1 Overview of examinations

Refer to the study flow chart in the synopsis for an overview of assessments and examinations required at each visit.

9.2 Data assessment and potential prognosis factors before the initiation of radiotherapy

The following parameters will be recorded at the start of the trial: medical history, concomitant diseases, physical examination, complications from head-and-neck surgery, age, date of birth, gender, body height and body weight, performance status (ECOG-PS, **Appendix IV**), site of primary tumor (oropharynx, oral cavity, hypopharynx and larynx), TNM-stage, AJCC-stage, histology (squamous cell carcinoma), HPV status (negative/positive), histologic grading (G1, G2, G3), surgery of primary tumor (no/yes), extent of resection (R0, R1, R2), neck dissection (no, unilateral, bilateral), complications of surgery, chemotherapy planned (no/yes, type of chemotherapy), Skin Status of the head-and neck region, and Quality of Life (EORTC QLQ-C30 Version 3.0 and EORTC QLQ-H&N35)**.**

9.3 Examinations with relation to primary and secondary aim criteria

The following parameters will be assessed continuously throughout the course of the trial:

9.3.1 Radiation dermatitis

Radiation dermatitis will be assessed daily by two independent observers (specially trained nurses, technicians, or physicians), daily during radio(chemo)therapy and up to three weeks following radio(chemotherapy) according to CTCAE v4.03 **(Appendix III)**. If the graduation of radiation dermatitis varies between the two observers, skin toxicity will be assessed by an additional observer. Observers are required to be very experienced in rating skin reactions and will additionally undergo a particular briefing prior to the start of this study.

9.3.2 Adverse Events

Adverse events, other than radiation dermatitis will be assessed on an ongoing basis according to CTCAE v4.03. The documentation is described in section 8.2.

9.3.3 Quality of life

Quality of life will be assessed prior to radio(chemo)therapy, at the end of radiotherapy weeks 3 and 5, as well as three weeks following radio(chemo)therapy using the EORTC QLQ-C30 Version 3.0 and the EORTC QLQ-H&N35.

9.3.4 Pain assessment

Pain (radiation fields) is assessed with a visual analogue scale (self assessment: from 0 = No pain; 1 = Mild pain to 10 = Very severe pain). In addition, pain scores will be correlated with the grade of skin reactions.

10 Statistics

10.1 Sample size calculation

The primary goal of this randomized trial is to demonstrate that Mepitel® Film is superior to Standard Care with respect to prevent grade ≥2 radiation dermatitis in patients receiving radio(chemo)therapy up to 50 Gy for locally advanced SCCHN.

The null hypothesis of equal rates of grade ≥2 skin toxicity is tested against the two-sided alternative hypothesis of different rates. Based on this hypothesis system, the sample size required for this trial is calculated taking into account the following assumptions:

- A Chi-square Test will be applied
- The two-sided significance level is set to 5%
- In patients treated with radio(chemo)therapy for locally advanced SCCHN, previous studies have suggested rates of grade ≥2 skin toxicity of 86-92% if standard skin care was administered.
- Based on these data, a rate of grade ≥2 skin toxicity of 85% can be assumed in the reference group ("worst-case"), i.e. in patients receiving standard care for skin toxicity.
- Administration of Mepitel® Film will be considered to be clinically relevant, if the rate of grade ≥2 skin toxicity can be reduced to 65%.
- The power to yield statistical significance if the the difference in rates is in fact 20 percentage points is set to 80%.

Based on these assumptions, 80 patients are required per study arm within the Full Analysis Set. Taking into account that 5% of patients will not qualify for Full Analysis Set, a total of 168 patients should be randomized.

10.2 Analysis Sets

Full Analysis Set

The Full Analysis Set includes all randomized patients who have started either therapy with arm A or with arm B. The Full Analysis Set will be analyzed according to the Intent-to-Treat principle, i.e. patients will be analyzed in their initial group of randomization.

Per Protocol Set

The Per Protocol Set will comprise all patients of the Full Analysis Set and will exclude patients if any of the following criteria are met:

- Administration of less than 50 Gy if the reason for discontinuation was any other than death or unacceptable toxicity
- Delay of radiotherapy for more than 7 days prior to reaching 50 Gy

All patients in the Per Protocol Set will be analyzed within their group of actual treatment received.

10.3. Statistical analysis

General Considerations

All data recorded in the case report forms describing the study population, toxicity and quality of life will be analyzed descriptively. Categorical data will be presented in contingency tables with frequencies and percentages. Continuous data will be summarized with at least the following: frequency (n), median, quartiles, mean, standard deviation (standard error), minimum and maximum. Number of patients with protocol deviations during the study and listings describing the deviations will be provided.

In general, chi-square tests will be used to compare percentages in a two-by-two contingency table, replaced by Fisher´s exact test if the expected frequency in at least one cell of the associated table is less than 5. Stratified two-by-two contingency tables will be analyzed using Cochran-Mantel-Haenszel tests. Logistic regression models serve as multivariable methods for binary endpoint data. Comparison of ordinal variables between treatment arms will be performed using the asymptotic Wilcoxon-Mann-Whitney test, replaced by its exact version in case of ordinal categories with small number of categories and/or sparse data within categories. Any shift in location of quantitative variables between study groups will be performed with Wilcoxon-Mann-Whitney tests as well.

Time-to-event data will be analyzed by Kaplan-Meier methods, when merely non-informative censoring occurs. For statistical comparison, the logrank-test will be provided supplemented by multivariate Cox proportional hazards models.

The data analysis will be performed according to the statistical analysis plan (SAP), and which will be finalised prior to database lock and prior to any statistical analysis.

Primary Endpoint

The rates of patients experiencing grade ≥2 radiation dermatitis in patients receiving radio(chemo)therapy up to 50 Gy will be statistically compared using the Cochran-Mantel-Haenszel Chi-square test on a two-sided significance level of 5%. This test is the natural non-parametric extension of the Chi-square test for testing the treatment effect, while adjusting for the effects of the stratification variables used for randomization. For further assessment of the robustness of the results, a logistic regression model for grade ≥2 radiation dermatitis will be applied including the parameters used for stratification. In addition, a model including also additional patient characteristics will be fitted.

The confirmatory evaluation will be performed within the Full Analysis Set, the Per Protocol Set serves for further sensitivity analyses.

Secondary endpoints

Time to grade 2 radiation dermatitis until 50 Gy of radiotherapy is defined as the time from start of radiotherapy to at least grade 2 radiation dermatitis. Patients without grade 2 radiation dermatitis will be censored after the date of receiving a total dose of 50 Gy. Rate of grade ≥2 dermatitis at 60 Gy and at the end of radiotherapy will be evaluated.

The distribution of the time to grade 2 radiation dermatitis until administration of 50 Gy will be described using Kaplan-Meier methods. These analyses will be stratified by treatment arm and prognostic risk groups used for randomization. Estimates of median time to grade 2 radiation dermatitis and estimates of rates for specific time points will be extracted from the

Kaplan-Meier analyses together with the associated 95% confidence limits. The treatment differences will be tested using a stratified log-rank test, stratified by stratification factors. Furthermore, Cox proportional hazards models will be applied to yield adjusted estimates of the associated hazard ratios.

The methods used for statistical analysis of rate of patients experiencing grade ≥2 radiation dermatitis during radio(chemo)therapy and rate of patients experiencing grade ≥3 skin toxicity during radio(chemo)therapy matches those already described for the primary study endpoint.

All other adverse events as reported according to CTCAE v4.03 will also be subjected to statistical analysis. Adverse event tables will be created. These tables will present the total number of patients reporting at least one specific event and the maximum CTCAE grade. Thus, patients reporting more than one episode of the same event will be counted only once by the worst CTCAE grade per patient. Special tables will be displayed for CTCAE Grade III/IV/V adverse events. Additionally, analysis will be restricted to treatment related adverse events and treatement related CTCAE Grade III/IV/V events.

Quality of life will be evaluated using the validated EORTC QLQ-C30 and EORTC QLQ-H&N35 questionnaires. Data will be scored according to the algorithm described in the respective scoring manuals. For all quality of life domains and items, descriptive analyses will be presented stratified by visit and treatment arm.

For descriptive statistical analysis, summary tables will be provided showing measures of location and dispersion (minimum, quartiles, median, maximum, mean and standard deviation) stratified by visit and treatment arm. Furthermore, individual score items will be subjected to statistical analysis. Absolute changes of QoL-scores from baseline will be tabulated stratified by treatment group and visit. For graphical illustrations, Box-Whisker diagrams will be presented across visits for each treatment group. Nonparametric (exact) Wilcoxon-Mann-Whitney tests will be applied for exploratory comparison purposes. Additional details of the QoL analysis will be described in the SAP.
In case of uneven distribution to stratification groups, which may result in very small groups the strata might be connected for analysis. The decision to merge strata for the analysis will be made before data base lock and before the final analysis of the data.

Interim analysis

To evaluate the tolerance and acceptance of the Mepitel® Film treatment after one third of the study an interim analysis will be conducted after inclusion of 57 patients. The recruitment will be put on hold until the 57 patients have completed the study. Depending on the proportion (i.e. ≥ 25%) of patients who did not tolerate or accept Mepitel® Film, the study will be continued or discontinued. Furthermore, the skin toxicity between both treatment groups will be compared.

The same procedures will be followed as described for the final analysis of the study.

11. Ethical and legal principles

The examinations to be carried out as part of this trial are all considered standard procedures. There are no additional laboratory investigations or X-rays to be done, or any other examinations that could be potentially burdensome for the patient.

11.1 Ethics committee vote

The trial protocol will be submitted to the ethics committee responsible. The positive vote of the ethics committee must be communicated to the trial management along with the names and qualifications of the ethics committee members.

11.2 Patient information and informed consent

Patient information and informed consent will be submitted along with the trial protocol for evaluation by the ethics committee responsible. Before inclusion in the trial, each patient will be fully informed about the content and procedure of the trial (Appendix I).

If the potential trial patient has received the necessary information and if the investigator is sure that the patient has understood this information, the patient will be asked to give their consent by signature (Appendix II).

The patient will receive a copy of the patient information and the signed informed consent form. The investigator must also inform the patient that he/she has the right to withdraw consent to participate in the trial at any time and without having to give any reasons. Patients must be informed that the data collected as part of the trial will be documented anonymously and will then be forwarded for scientific evaluation. This is also the appropriate point to indicate the patient consent to data protection.

11.3 Declaration of Helsinki

The trial will be conducted in accordance with the principles laid out in the Declaration of Helsinki.

11.4 Data protection

Data will be collected in accordance with the regulations set out in the Data Protection Act. All findings from the clinical trial will be stored on electronic data storage devices and treated with utmost confidentiality. Organization measures have been taken in order to prevent the data from being communicated to unauthorized persons. Patients will only be identified via their individual patient numbers throughout the entire documentation and evaluation phase and their full name will not be used.

11.5 Trial registration

The trial will be registered in one of the primary registers accepted by the WHO. The trial will not start prior to successful registration.

11.6 Protocol amendments

Amendments to the study protocol may only be implemented if again approved by the responsible ethics committee. Only the coordinating principal investigator may carry out such changes. However, all co-investigators should contact the coordinating principal investigator if modifications seem to be necessary. In case of changes to the study protocol, all investigators will be informed after ethics committee approval and the notice has to be confirmed.

12. Data management

12.1 Patient identification list

All data relating to patients will be recorded in a pseudonymous way. Each patient will be identifiable only by the unique patient number, date of birth and gender. A patient identification list will only be kept in the relevant trial centers and will not be forwarded to the sponsor.

12.2 Documentation sheet

Data collection will be done using the data documentation sheets**.**

The data documentation sheets must be filled in using a ballpoint pen. Do not use fountain pens or pencils. Corrections must be made as follows: cross the error out once with a straight line, enter the correct information next to it and note the date and/or reason for correction. Comments must be made if data fields cannot be filled in because of missing information.

The sheets should be filled in as soon as possible and should be submitted to the checker for review, signed, dated and forwarded to the trial management.

12.3 Storage of trial documents

The originals of all key trial documents, including the documentation sheets, will be kept at the trial headquarters (i.e. the sponsor responsible for the trial) for a minimum of 15 years after the final report.

The principal investigator/head of the trial centre will keep all administrative documents (written correspondence with the ethics committee, regulatory authorities, trial management, trial headquarters), the patient identification list, the signed informed consent forms, copies of the documentation sheets and the general trial documentation (protocol, amendments) for the abovementioned period. Original patient data (patient files) must also be kept for the length of time stipulated for the trial centers, but not for less than 15 years.

13. Quality Assurance

13.1 Monitoring

The ZKS Lübeck will conduct clinical on-site monitoring at the German sites according to GCP and written standard operating procedures (SOPs) to ensure the patients' rights and safety as well as the reliability of trial results.

For initiation, trial sites will be visited on-site by a clinical research associate of the ZKS Lübeck. During the trial, sites will be visited at regular intervals depending on the rate of recruiting and data quality. Informed consent and defined key data will be checked of all patients. The medical file of each patient will be screened for adverse and serious adverse events. Patients' questionnaires will be checked for their existence.

According to SOPs, all trial specific monitoring activities will be defined before starting the trial and documented in writing (monitoring manual).

The Danish sites will be monitored according to the Danish regulations in their own responsibility.

13.2 Audits

No regular audits are planned. However, to ensure correct execution of the study, audits may be conducted if necessary.

13.3 Inspections

As the current study is not linked to the German pharmaceutical or medicinal product act, no inspections of higher federal authorities are scheduled.

14. Dissemination of Results and Publication Policy

The coordinating principal investigator will work towards comprehensive internal and external dissemination of project results and knowledge. Coordinating principal investigator, biostatistician and reference centers will create a report according to the CONSORT statement regardless of regular or abnormal study termination.

The scientific results will be published in international, peer-reviewed journals of the highest possible quality. In addition, results will be presented at major medical congresses and symposia.

Due to methodological and statistical aspects results will be published only after study database closure. All reports and publication related to the study need to be coordinated with the biostatistician to avoid misinterpretation of statistical results. Conclusions need to be statistically secured and require approval of the statistician.

The local centers are entitled to use the recorded data for additional scientific exploitation under their own name, but not before the main results have been published. There are no exceptions to this rule. Any sub-publication requires approval by the coordinating principal investigator. For publications of any kind the study acronym RAREST-01 will be used.

15. References

1. Rades D, Kronemann S, Meyners T, Bohlen G, Tribius S, Kazic N, Schroeder U, Hakim SG, Schild SE, Dunst J. Comparison of four cisplatin-based radiochemotherapy regimens for nonmetastatic stage III/IV squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2011;80:1037-44.

2. Rades D, Stoehr M, Kazic N, Hakim SG, Walz A, Schild SE, Dunst J. Locally advanced stage IV squamous cell carcinoma of the head and neck: impact of pre-radiotherapy hemoglobin level and interruptions during radiotherapy. Int J Radiat Oncol Biol Phys 2008;70:1108-14.

3. Fesinmeyer MD, Mehta V, Blough D, Tock L, Ramsey SD. Effect of radiotherapy interruptions on survival in medicare enrollees with local and regional head-and-neck cancer. Int J Radiat Oncol Biol Phys 2010;78:675-81.

4. Rades D, Fehlauer F, Wroblesky J, Albers D, Schild SE, Schmidt R. Prognostic factors in head-and-neck cancer patients treated with surgery followed by intensity-modulated radiotherapy (IMRT), 3D-conformal radiotherapy, or conventional radiotherapy. Oral Oncol 2007;43:535-43.

5. Rades D, Stoehr M, Meyners T, Bohlen G, Nadrowitz R, Dunst J, Schild SE, Wroblewski J, Albers D, Schmidt R, Alberti W, Tribius S. Evaluation of prognostic factors and two radiation techniques in patients treated with surgery followed by radio(chemo)therapy or definitive radio(chemo)therapy for locally advanced head-and-neck cancer. Strahlenther Onkol 2008;184:198-205

6. Diggelmann KV, Zytkovicz AE, Tuaine JM, Bennett NC, Kelly LE, Herst PM. Mepilex Lite dressings for the management of radiation-induced erythema: a systematic inpatient controlled clinical trial. Br J Radiol 2010;83:971-8.

7. Santamaria N, Gerdtz M, Sage S, McCann J, Freeman A, Vassiliou T, De Vincentis S, Ng AW, Manias E, Liu W, Knott J. A randomised controlled trial of the effectiveness of soft silicone multi-layered foam dressings in the prevention of sacral and heel pressure ulcers in trauma and critically ill patients: the border trial. Int Wound J 2013, in press.

8. Silverstein P, Heimbach D, Meites H, Latenser B, Mozingo D, Mullins F, Garner W, Turkowski J, Shupp J, Glat P, Purdue G. An open, parallel, randomized, comparative, multicenter study to evaluate the cost-effectiveness, performance, tolerance, and safety of a silver-containing soft silicone foam dressing (intervention) vs silver sulfadiazine cream. J Burn Care Res 2011;32:617-26.

Appendix I Patient Information

Please refer to seperate document ‚Patienteninformation‘.

Appendix II Informed Consent

Please refer to seperate document ‘Einwilligungserklärung‘.

Appendix III

Radiation Dermatitis according to CTCAE v4.03

Grade 1: - faint erythema or dry desquamation

Grade 2: - moderate to brisk erythema
- patchy moist desquamation, mostly confined to skin folds and creases
- moderate edema

Grade 3: - moist desquamation in areas other than skin folds and creases
- bleeding induced by minor trauma or abrasion

Grade 4: - life-threatening consequences
- skin necrosis or ulceration of full thickness dermis
- spontaneous bleeding from involved site
- skin graft indicated

Grade 5: - death

Appendix IV

Eastern Cooperative Oncology Group (ECOG) – Performance Score

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