# ATELIER : idées reçues sur la prévention et la prise en charge des complications des traitements

## Gestion de la radiodermite : idées reçues et actions efficaces

**Marc Bollet, Paris**

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# Radiodermites aiguës

**Enjeux**

- **la compliance**
- **la QdV**

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# LES FACTEURS DE RISQUE

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# Radiodermite - facteurs de risque
## radiothérapie

- Effet dose

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# Les facteurs de risque
# la radiothérapie effet dose

**Table 4 Multivariate analysis for G2+ dermatitis and moist desquamation** **377 pts**

| Clinical/genetic factor | Acute G2+ dermatitis | | Moist desquamation | |
|---|---|---|---|---|
| | OR | p-value | OR | p-value |
| **Center** (CMSE vs. GUH) | - | - | 3.206 | 0.158 |
| **BMI** | **1.088** | **0.003** | **1.170** | **<0.001** |
| **Bra cup size** (cup ≥ D vs. cup A + B + C) | **2.833** | **0.001** | **2.146** | **0.043** |
| **Smoking** (yes vs. no) | **2.711** | **0.010** | - | - |
| **Fractionation** (hypo vs. normo) | **0.083** | **<0.001** | **0.096** | **<0.001** |
| **Treatment position** (prone vs. supine) | **0.399** | **0.004** | 0.373 | 0.074 |
| **Hormone therapy** | | | | |
| No | 1 | | 1 | |
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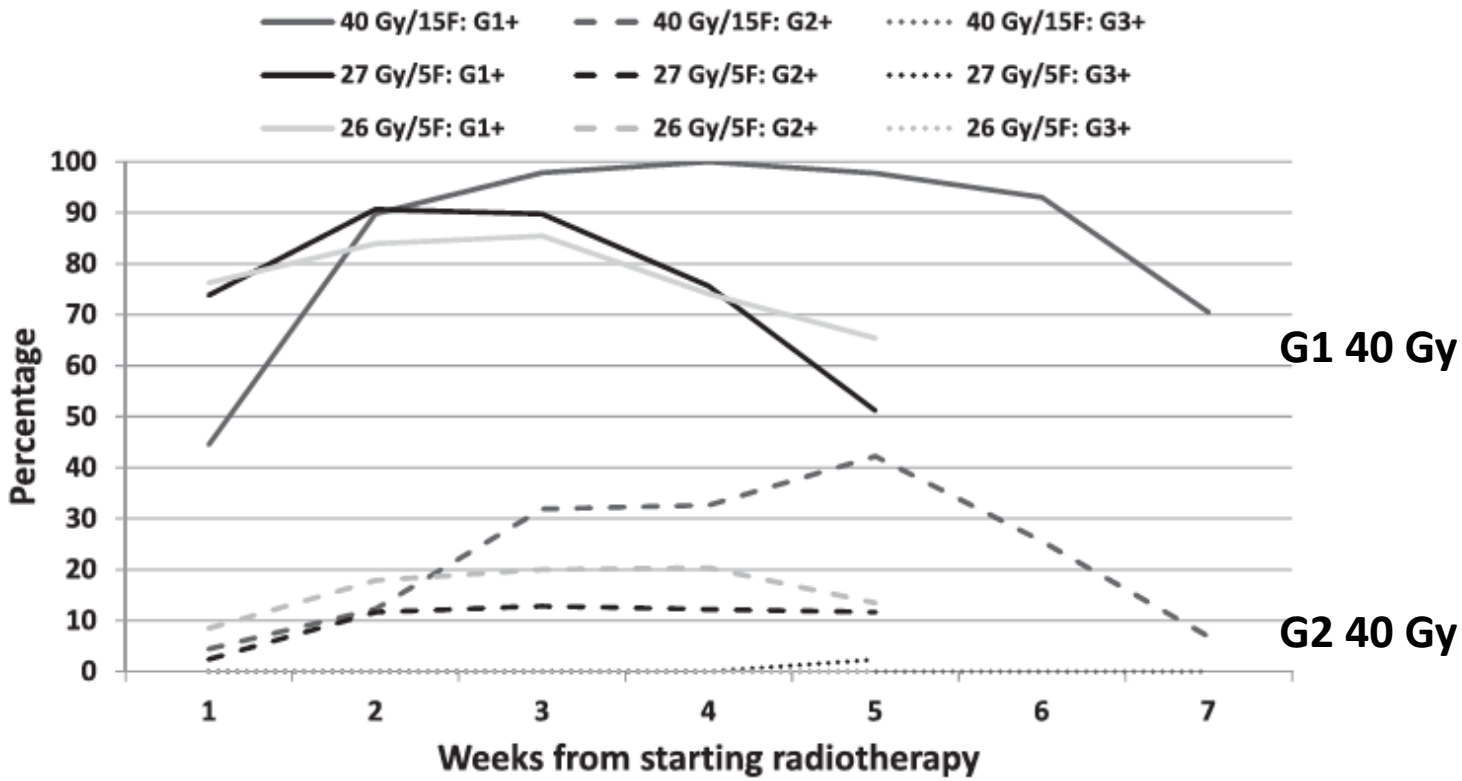
| **Nodal irradiation** (yes vs. no) | 1.975 | 0.100 | - | - |
| **Chemotherapy** (yes vs. no) | 0.954 | 0.877 | - | - |
| **Trastuzumab** (yes vs. no) | **0.177** | **<0.001** | - | - |
| ***MLH1* rs1800734 G > A** | | | | |
| GG | 1 | | - | |
| GA | **0.492** | **0.008** | - | - |
| AA | 0.537 | 0.232 | - | - |

**Effet protecteur lié à moindre dose totale**

De Langhe et al. BMC Cancer 2014

# Les facteurs de risque
# la radiothérapie effet dose

*UK FAST-Forward Trial*




Grade 3 toxicity reported at 4 weeks post-RT in 27 Gy/5F patient resolved to grade 1 one week later

**Fig. 1.** Acute toxicity substudy 2 – Prevalence of grade 1+, grade 2+ and grade 3+ CTCAE toxicity.

Brunt radiotherOncol2016

# Radiodermite - facteurs de risque
## radiothérapie

- Effet dose
- Effet volume
- Effet localisation (plis+++)
- Effet rayonnement (Cobalt, E RX et $e^-$)
- Effet technique (homogénéité)

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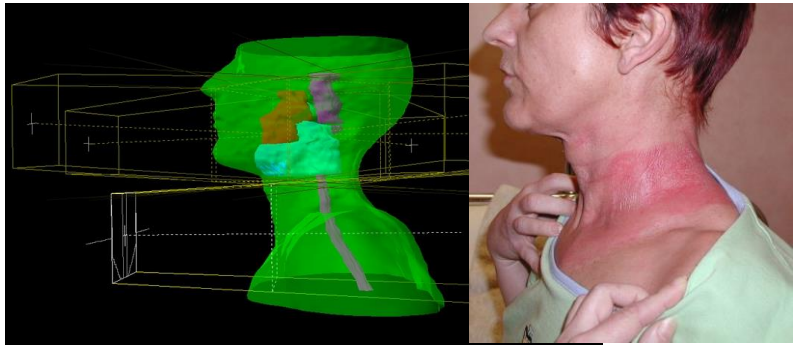
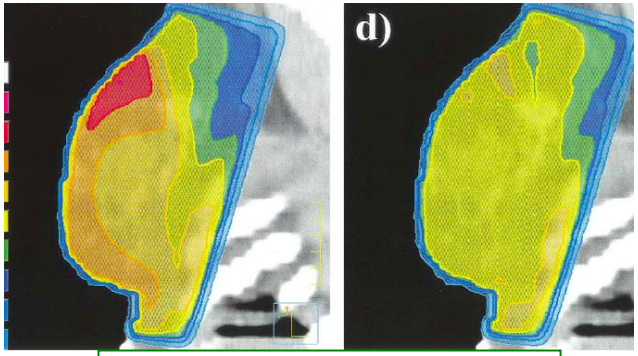
# Les facteurs de risque
# la radiothérapie effet technique

## Gagner en homogénéité






Vicini et al.IJROBP 2002

| first author | location | journal | year | n pts | years | Primary endpoint | results |
|---|---|---|---|---|---|---|---|
| Donovan | RMH | R&O | 2007 | 306 | 1997-2000 | late change | S |
| Pignol | Canada | JCO | 2008 | 342 | 2003-2005 | acute dermatitis | S |
| Barnett | Cambridge | IJROBP | 2011 | 1145 | 2003-2007 | fibrosis (photo) at 2 years | NS |

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# Les facteurs de risque intrinsèques

- Génétique

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# Les facteurs de risque
# intrinsèques Génétiques

- Pathogènes (AT, Li Fraumeni, …)
- Variations génétiques ex MLH1 rs1800734

De Langhe et al. BMC Cancer 2014

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# Les facteurs de risque intrinsèques Génétiques

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# Les facteurs de risque intrinsèques Phototype

**Table 7.** Incidence of Grade 2 radiodermatitis according to skin phototype at week 5.

| | | Skin phototype | | | |
|---|---|---|---|---|---|
| | | IV ($N$ = 25) | | V ($N$ = 25) | |
| Grade 2 radiodermatitis | NO | 13 | 52% | 15 | 20% |
| | YES | 12 | 48% | 20 | 80% |
| Total | | 25 | 100% | 25 | 100% |

95% confidence interval for the difference of the two proportions (.0691, .5709), p-value = 0.0092.



Meghrajani et al Expert Review of Clinical Pharmacology 2016

# Les facteurs de risque intrinsèques Phototype

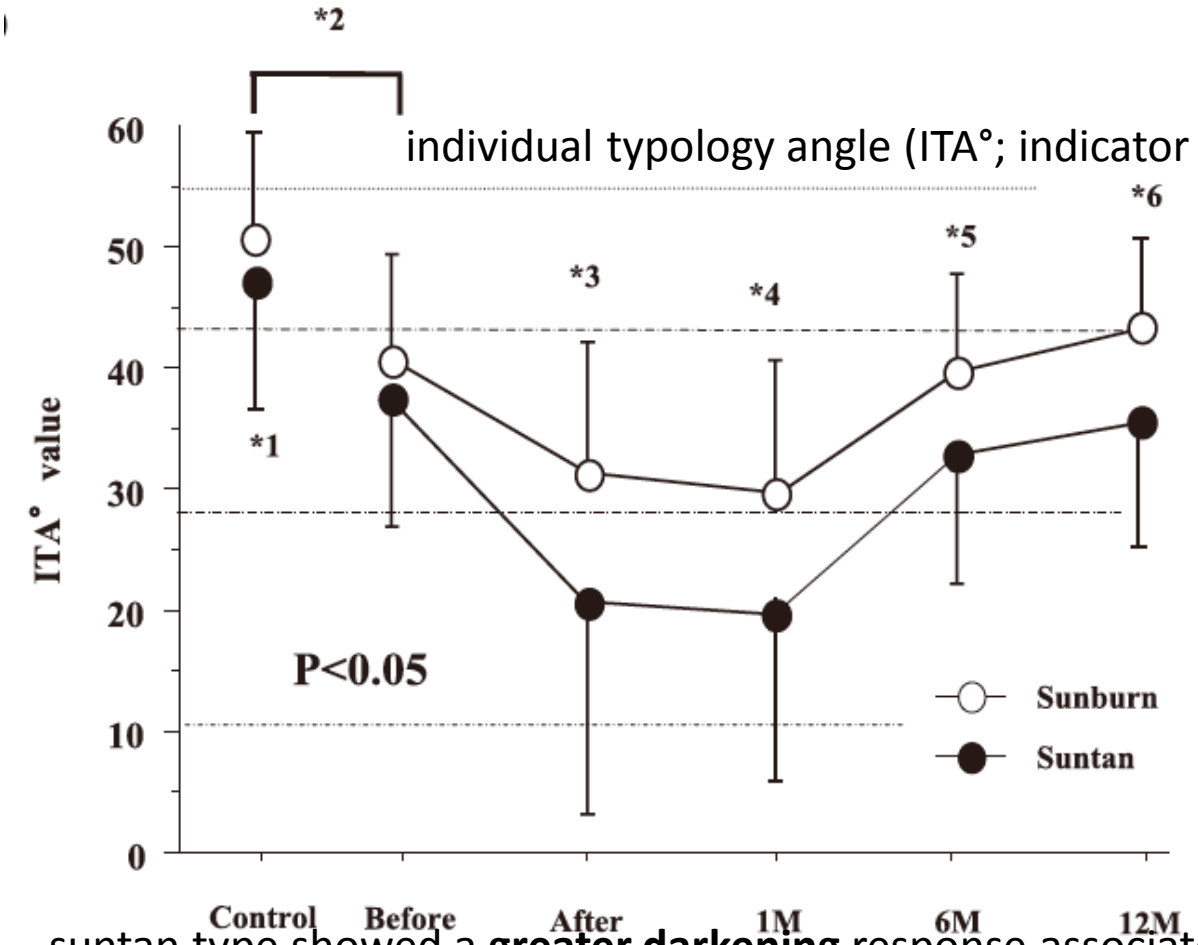
By CTCAE v3 classifications, **a Grade 2** reaction appeared **in 14% sunburn patients** and in **31% of the suntan group**, respectively **(*p* = 0.16**

Self-reported phototype has the potential to be a good predictor of skin sensitivity to radiation exposure for clinical screening



Yamazaki J Radiat Res 2011

# Les facteurs de risque intrinsèques Phototype




suntan type showed a **greater darkening** response associated with radiation dermatitis than did the sunburn type

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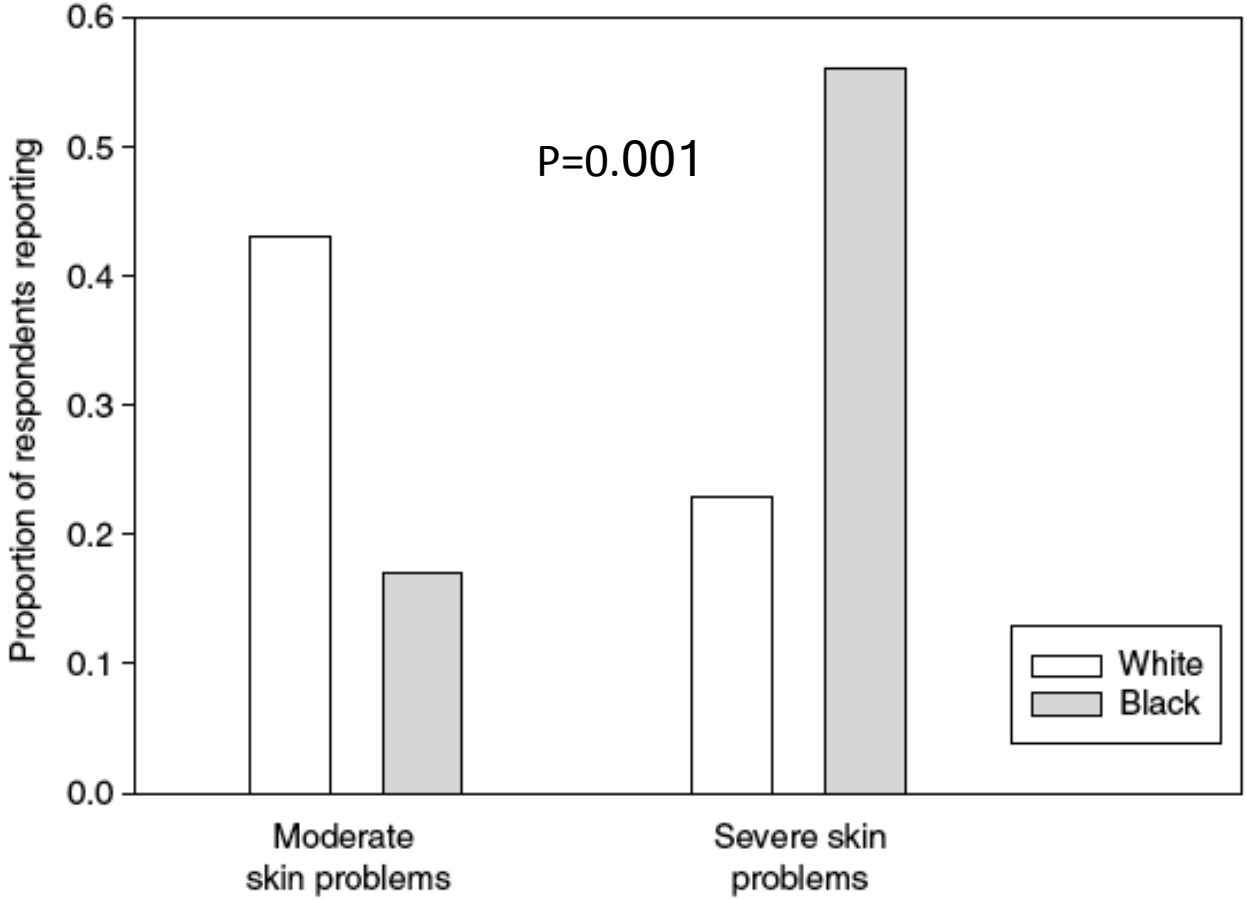
Yamazaki J Radiat Res 2011

# Les facteurs de risque intrinsèques Phototype

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Ryan BJC2007

# Les facteurs de risque intrinsèques Absence d'allergies

**Table 5 Results of the multivariate analysis (ordinal regression analysis) erythema G 0 versus erythema G 1 versus erythema G 2 at 50 Gy time point**

| | Estimate | SE | Wald | df | p | 95% CI |
|---|---|---|---|---|---|---|
| Breast volume [cc] (continuous) | .001 | .000 | 9.031 | 1 | .003 | .000; .002 |
| No allergies vs. allergies | 1.013 | .334 | 9.191 | 1 | .002 | .358; 1.669 |
| T1/2 vs T2/4 | 1.482 | 1.090 | 1.851 | 1 | .174 | −3.618; .653 |
| AHT aromatase inhibitors vs No AHT | .019 | .376 | .003 | 1 | .959 | -.718; .757 |
| AHT aromatase inhibitors vs No AHT | -.265 | .455 | .341 | 1 | .559 | −1.156; .625 |
| No current Smoking vs current smoking | -.819 | .386 | 4.498 | 1 | .034 | −1.575; .062 |

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Kraus-Tiefenbacher et al RadiationOncology2012

# Les facteurs de risque intrinsèques

- Génétique
- Comorbidités (cardiovasculaires, diabète)

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# Les facteurs de risque

## intrinsèque Anatomique Volume sein

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De Langhe et al. BMC Cancer 2014

# Les facteurs de risque

# intrinsèque Anatomique IMC

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De Langhe et al. BMC Cancer 2014

# Les facteurs de risque

# intrinsèque Anatomique IMC

Factors related to severe acute radiation skin reactions.

| Factor | Events (%)/patients | Unadjusted | | Adjusted[a] | | Stepwise[b] | | Bootstrap[c] |
|---|---|---|---|---|---|---|---|---|
| | | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value | Inclusion % |
| Age | | | | | | | | |
| <50 years | 16 (18)/90 | 1 | 0.56[d] | 1 | 0.044[d] | | | 43 |
| 50–64 years | 37 (23)/161 | 1.4 (0.7–2.7) | | 2.2 (1.0–4.8) | | | | |
| ≥65 years | 30 (22)/139 | 1.3 (0.7–2.5) | | 2.7 (1.2–6.0) | | | | |
| BMI | | | | | | | | |
| Normal | 26 (15)/175 | 1 | <0.001[d] | 1 | <0.001[d] | 1 | <0.001[d] | 96 |
| Overweight | 28 (19)/147 | 1.4 (0.8–2.4) | | 1.1 (0.6–2.1) | | 1.4 (0.7–2.5) | | |
| Obese | 29 (43)/68 | 4.3 (2.3–8.1) | | 4.2 (2.1–8.3) | | 4.2 (2.2–8.3) | | |
| Smoking: CO-test detected | | | | | | | | |
| No | 70 (20)/352 | 1 | 0.059 | 1 | 0.031 | 1 | 0.027 | 55 |
| Yes | 11 (38)/32 | 2.1 (1.0–4.6) | | 2.5 (1.1–5.7) | | 2.5 (1.1–5.7) | | |
| Surgery | | | | | | | | |
| Partial mastectomy | 54 (18)/296 | 1 | 0.010 | 1 | 0.23 | | | 30 |
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| Seroma after surgery | | | | | | | | |
| No | 63 (20)/311 | 1 | 0.30 | 1 | 0.54 | | | 6 |
| Yes | 20 (26)/78 | 1.4 (0.8–2.4) | | 0.8 (0.4–1.7) | | | | |
| Dose | | | | | | | | |
| <50 Gy | 18 (15)/121 | 1 | 0.053 | 1 | 0.050 | 1 | 0.040 | 48 |
| ≥50 Gy | 62 (24)/263 | 1.8 (1.0–3.1) | | 1.9 (1.0–3.8) | | 1.9 (1.0–3.5) | | |
| Earlier chemotherapy | | | | | | | | |
| No | 41 (17)/243 | 1 | 0.007 | 1 | 0.054 | | | 45 |
| Yes | 42 (28)/147 | 2.0 (1.2–3.2) | | 1.8 (1.0–3.3) | | | | |
| Ongoing endocrine therapy | | | | | | | | |
| No | 37 (21)/176 | 1 | 0.91 | 1 | 0.52 | | | 9 |
| Yes | 46 (22)/214 | 1.0 (0.6–1.7) | | 1.2 (0.7–2.1) | | | | |

390 women from a randomised study in BC pts

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# Les facteurs de risque extrinsèques chimiothérapie

- Concomitante

| | Rouesse | | | | Arcosein | | | |
|---|---|---|---|---|---|---|---|---|
| | | Seq | Conc | p | | Seq | Conc | p |
| Epidermitis | Grade ≥2 | 21% | 29% | 0.03 | Grade ≥1 | 37% | 41% | NS |
| | Roxuesse et al. IJROBP 2006 | | | | Calais Cancer Radiothérapie 2004 | | | |

- Séquentielle ?

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# Les facteurs de risque extrinsèques hormonothérapie

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De Langhe et al. BMC Cancer 2014

# Les facteurs de risque extrinsèques Herceptin

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**Effet protecteur ?**

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# Les facteurs de risque extrinsèques Tabac

Data from a randomised study on 357 pts (H&N, Anal or Breast)

Estimates of the effect of treatment area, skin treatment and other factors on continuous outcomes from multivariate analysis

| Range | | RTOG mean (0–4) | | Erythema meter mean | | Mean diary score (0–3) | | Mean DLQI score (0–11) | |
|---|---|---|---|---|---|---|---|---|---|
| | | Difference from ref cat | 95% CI | Difference from ref cat | 95% CI | Difference from ref cat | 95% CI | Difference from ref cat | 95% CI |
| Smoking | Smoker | 0.32 | (0.19,.0.45) | 16.0 | (3.5, 28.5) | 0.24 | (0.07, 0.41) | 0.54 | (−0.26, 1.33) |
| | Ex smoker | 0.17 | (0.05, 0.29) | 15.1 | (3.9, 26.4) | 0.15 | (0.00, 0.30) | 0.05 | (−0.67, 0.77) |
| | Non smoker (ref cat) | – | | – | | – | | – | |
| *P* value | Comparing groups | <0.0001 | | 0.009 | | 0.016 | | 0.34 | |

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Wells et al RadiationOncology2004

# Les facteurs de risque extrinsèques Tabac

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| Ongoing endocrine therapy | | | | | | | | |
| No | 37 (21)/176 | 1 | 0.91 | 1 | 0.52 | | | 9 |
| Yes | 46 (22)/214 | 1.0 (0.6–1.7) | | 1.2 (0.7–2.1) | | | | |

390 women from a randomised study in BC pts

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Sharp TheBreast2013

# Les facteurs de risque extrinsèques Tabac

**Table 4 Multivariate analysis for G2+ dermatitis and moist desquamation**

| Clinical/genetic factor | Acute G2+ dermatitis | | Moist desquamation | |
|---|---|---|---|---|
| | OR | p-value | OR | p-value |
| **Center** (CMSE vs. GUH) | - | - | 3.206 | 0.158 |
| **BMI** | **1.088** | **0.003** | **1.170** | **<0.001** |
| **Bra cup size** (cup ≥ D vs. cup A + B + C) | **2.833** | **0.001** | **2.146** | **0.043** |
| **Smoking** (yes vs. no) | **2.711** | **0.010** | - | - |
| **Fractionation** (hypo vs. normo) | **0.083** | **<0.001** | **0.096** | **<0.001** |
| **Treatment position** (prone vs. supine) | **0.399** | **0.004** | 0.373 | 0.074 |
| **Hormone therapy** | | | | |
| No | 1 | | 1 | |
| Concomitant | **3.207** | **0.001** | **4.770** | **0.037** |
| Sequential (after IMRT) | 1.003 | 0.994 | 1.078 | 0.901 |
| **Nodal irradiation** (yes vs. no) | 1.975 | 0.100 | - | - |
| **Chemotherapy** (yes vs. no) | 0.954 | 0.877 | - | - |
| **Trastuzumab** (yes vs. no) | **0.177** | **<0.001** | - | - |
| ***MLH1* rs1800734 G > A** | | | | |
| GG | 1 | | - | |
| GA | **0.492** | **0.008** | - | - |
| AA | 0.537 | 0.232 | - | - |

De Langhe et al. BMC Cancer 2014

# LES MESURES À PRENDRE

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# Traitement de la radiodermite

## Faible niveau de preuve

relative lack of high-quality evidence to support specific management strategies.

Wong Support Care Cancer2013 guidelines

**Il n'y a pas assez de bonnes études cliniques**

- The methodological quality of the included studies varied, and methodological shortfalls in these reviews might create biases to the overall results or recommendations for clinical practice. An up-to-date high-quality SR in the prevention/management of radiation dermatitis is needed to guide practice

Chan IJROBP 2012

**Il n'y a pas assez de bonnes revues et de bons référentiels**

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# LES RÈGLES HYGIÉNO-DIÉTÉTIQUES

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# Etat des lieux

- Grande disparité
- Recommandations non étayées

An anonymous online survey investigating various aspects of radiotherapy skincare management was distributed to departments across Europe and the USA (*n* = 181/737 responded i.e. 25%).



Odonovan European J of Cancer Care 2015

# Règles hygiéno-diététiques

- Eviter facteurs irritants cutanés
- mécaniques (rasage, frottements, tissus synthétiques, macération
- thermiques / solaires
- chimiques avec alcool…

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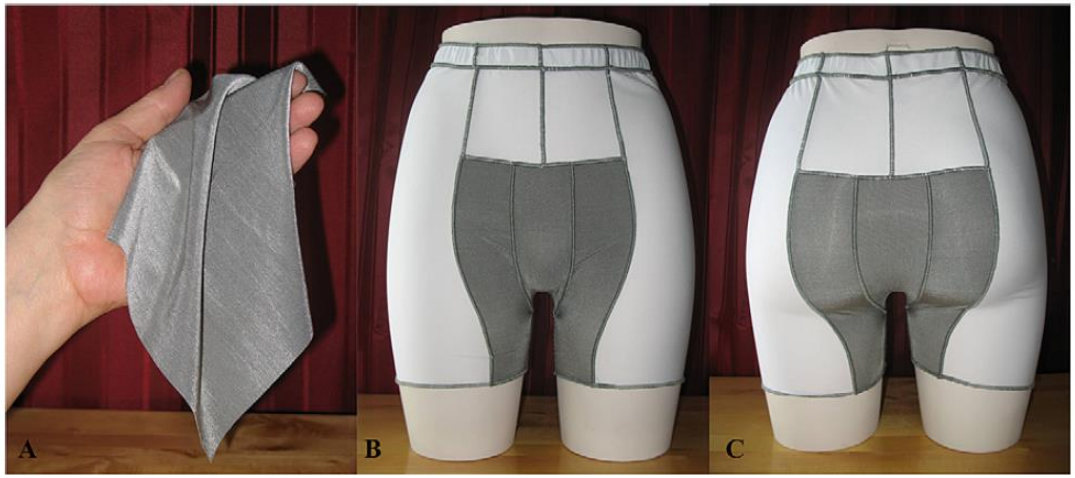
# Traitement préventif de la radiodermite
## silver clear nylon dressing (SCND)

- Positive  Rando 42 pelvic cancer pts

Niazi IJROBP2012




On the last day of treatment, the **mean dermatitis score**
standard arm was 2.53 (standard deviation [SD], 1.17)
SCND arm was 1.67 (SD, 1.2)**. P=0.01.**

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# Règles hygiéno-diététiques

- Eviter facteurs irritants cutanés
- mécaniques (rasage, frottements, tissus synthétiques, macération
- thermiques / solaires
- chimiques avec alcool…
- Bien s’hydrater
- Supplémentation alimentaire ?

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# Traitement préventif de la radiodermite
## supplémentation alimentaire

- Positive 40H&N pts with CTRT HMB.Arg.Gln

Imai JJCO2014

The incidence of Grade 3 dermatitis did not differ between the two groups.
However, as secondary endpoints of this study, the incidence of Grade 2 dermatitis was lower in Group A than B (**62.6 vs. 94.4**%; P<0.05), and the duration of Grade 1 & Grade 2 dermatitis was shorter in Group A than B (P< 0.05).

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# Règles hygiéno-diététiques

- Eviter facteurs irritants cutanés
- mécaniques (rasage, frottements, tissus synthétiques, macération
- thermiques / solaires
- chimiques avec alcool…
- Bien s’hydrater
- Supplémentation alimentaire ?
- Se laver (savon doux / sécher en tamponnant

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# Règles hygiéno-diététiques
## laver ou non ?

**4 randomized studies:**
**strong recommendation for gentle washing with water, with or without a mild soap/shampoo. (Level of evidence II, Recommendation Grade B)**



Wong Support Care Cancer2013 MASCC

# Règles hygiéno-diététiques

## Quel savon ?

Mild soaps and radiotherapy: a survey of the UK public to identify brands of soap considered mild and analysis of these to ascertain suitability for recommendation in radiotherapy departments

K. ROBERTSON, BSC, *The Beacon Centre, Taunton & Somerset NHSFT, Musgrove Park Hospital, Taunton,* &
P. BROWN, PHD, *Radiography Department, School of Healthcare Studies, Cardiff University, Cardiff, UK*

ROBERTSON K. & BROWN P. (2011) *European Journal of Cancer Care* **20**, 315–321

Only *Simple* and *E45* fit the cancer agencies' definition of mild soap and could therefore be recommended for radiotherapy patients

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# Règles hygiéno-diététiques
# déodorant ?

Four trials, no evidence to suggest that the use of antiperspirants resulted in increased toxicities.

**strong recommendation to allow the use of antiperspirants during breast radiotherapy. (Level of evidence I, Recommendation Grade A)**

# LES TRAITEMENTS

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# Traitement préventif de la radiodermite
## émollients

- Negative
  - RTOG 97-13 (172 BC pts) Trolamine (Biafine®)

    Large-breasted women receiving Biafine were more likely to have no toxicity 6 weeks post RT.

    Fisher IJROBP 2000
  - RTOG99-13 (547 H&N pts)

    Elliott JCO 2006

    The use of 15 different local standards of care highlights the need to continue research

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# Règles hygiéno-diététiques
# Effet délétère de certains émollients ?

**that aqueous cream BP is not meant to be used as a leave-on emollient Applying it routinely during radiotherapy may, therefore, be doing more harm than good.**
Aqueous cream is a cheap, highly effective cleansing and foaming agent.

SLS is known to be an irritant and it impairs skin barrier function Cetostearyl alcohol is a fatty alcohol present in creams. It is a potential cause of allergic contact dermatitis.

**In 2007, the National Institute for Health and Clinical Excellence (NICE) published guidelines stating that aqueous cream should not be used as a leave-on emollient, especially where skin barrier function was impaired.**



Patel ClinicalOncology2013

# Traitement préventif de la radiodermite
# hyaluronic acid

- Deleterious vs petrolatum gel (74pts early closure)

Pinnix IJROBP2014

The study closed early on the basis of a recommendation from the Data and Safety Monitoring Board after 74 of the planned 92 patients were enrolled. Breast skin treated with the hyaluronic acid gel developed a significantly higher rate of Grade 2 dermatitis than did skin treated with petrolatum gel: 61.5% (40/65) vs. 47.7% (31/65) (p=0.027)

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# Traitement préventif de la radiodermite

## aloe vera

- Negative rando 194 pts (double blind)

  Williams IIJROBP1996

  108 pts

- Delétère 225 pts vs Aqueous Cream

  Heggie Cancer Nurs 2001

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# Traitement préventif de la radiodermite

## calendula

- Positive vs Trolamine (254pts)

  grade≥ 2 (41% *v* 63%; *P*< .001) Pommier JCO

  vs Essential Fatty Acids (51pts)

  Schneider Rev Esc Enferm USP · 2015

- Negative vs aqueous cream (Essex) 420 pts

  Sharp European Jof Oncology Nursing2013

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# Traitement préventif de la radiodermite
## allantoine

- Negative vs aqueous cream 174 pts

Chan IJROBP2014

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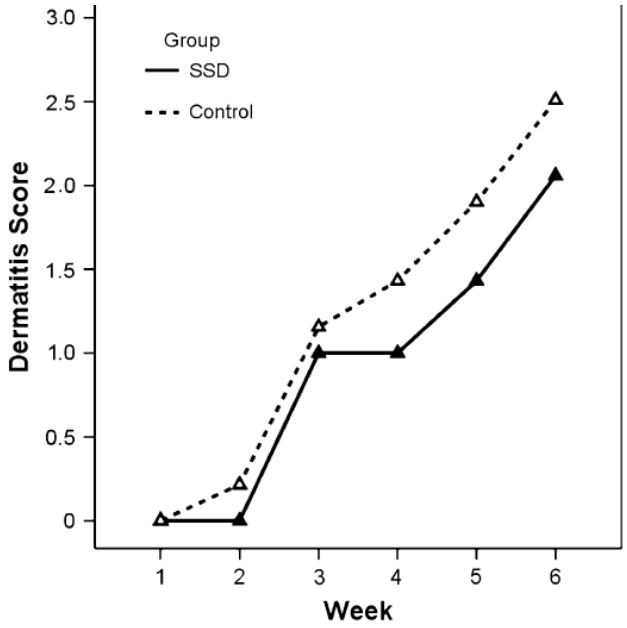
# Traitements préventifs de la radiodermite
## silver sulfadiazine (flammazine)

- Positive rando 102 pts

Hemati Support Care Cancer 2012



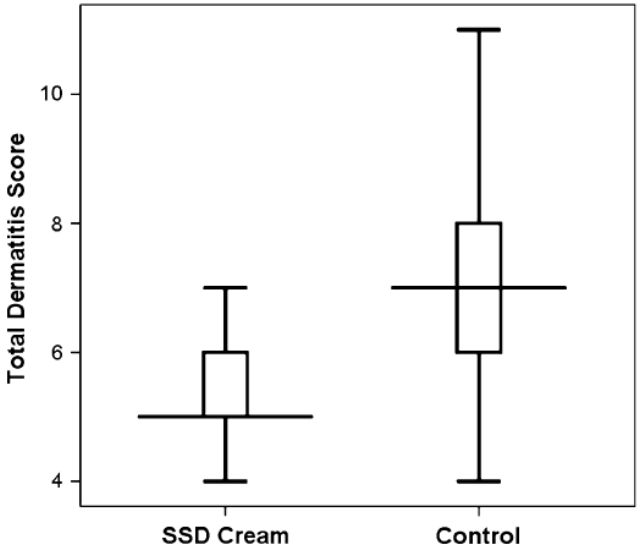




**Fig. 2** Comparison of the total dermatitis score between the two groups; $p<0.001$

**Absence d'objectif principal**

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# Traitement préventif de la radiodermite

## LED photomodulation

- Rando 33 pts: Negative

Fife DermatologicSurgery2010

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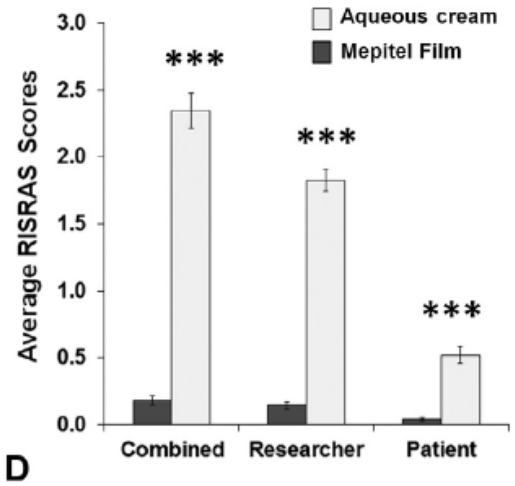
# Traitement préventif de la radiodermite
## soft silicone dressings

- Positive 78 pts: Mepitel


Herst RadiotherOncol 2014




P<0.0001

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# Traitement symptomatique de la radidermite grade 1 - émolients

- Positive heparinoid moisturizer vs placebo:

  improved water content

  Sekiguchi JJCO2015

  oil in water emulson

  enhanced stratum corneum hydration, improved clinical indicators, and provided relief from itching

  Jensen Strahlenter Onkol 2011

- Negative Hydrosorb vs water spray

  Bazire Radiother Oncol 2015

**Absence de bénéfice clinique**

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# Traitements symptomatiques grade 2 - dermocorticoïdes

- Vs moisturizer: potent steroid cream better (104pts)

Ulff et al Radiother Oncol 2016

- Vs placebo:

Meghrajani et al Expert Review of Clinical Pharmacology 2016

Postitive studies

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# Traitement préventif de la radiodermite
## synthèse

- The adoption of **washing** with water, with or without a mild soap, and allowing the use of **antiperspirants** is supported by randomized trials.

- Use of **topical** prophylactic **corticosteroids** (mometasone) is recommended to reduce discomfort and itching.
- There is some evidence that **silver sulfadiazine** cream can reduce dermatitis score.
- There **is insufficient evidence to support, and therefore the panel recommends against the use of** trolamine, topical sulcrate, hyaluronic acid, ascorbic acid, silver leaf dressing, light-emitting diode lasers, Theta cream, dexpanthenol, calendula, proteolytic enzymes, sulcralfate,oral zinc, and pentoxifylline.

# LES SOINS ALTERNATIFS

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# Les soins alternatifs

- Complementary & Alternative Medicine (CAM) Multicentric 360 USA pts

During breast cancer radiotherapy

  - CAM usage: **>50%** of the study cohort (194/360).
  - Of CAM users
    - 71% reported activity-based CAM (Reiki, meditation…)
    - 26% topical CAM
    - 45% oral CAM.
    - Only 16% received counseling from professionals
- CAM use significantly correlated with
  - **higher education level** (P<.001),
  - Absence of concomitant hormone/radiation therapy use (P=010)
  - A trend toward greater use in **younger** patients (PZ.066).
  - Significantly **lower skin toxicity** scores were reported in CAM users vs nonusers, respectively (mild: 34% vs 25%, severe: 17% vs 29%, P=017).



Moran et al IIJROBP2013

# L’INNOVATION

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# Prévention de la radiodermite /modèle animal

**Toll-like Receptor 5 Agonist**

Burdelya et al IJROBP 2012

**SuperOxyde Dismutase**

Doctrow J Invest Dermatol2013

**Topical vasoconstrictor**

Fahl IntJCancer2014

**Inhalation of hydrogen gas**

Watanabe Journal of Radiation Research2014

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# Conclusions

- L'incidence de la radiodermite diminue (désescalade thérapeutique, meilleur ratio thérapeutique)
- Sa prise en charge est importante (compliance et qualité de vie)
- Il est important d'estimer le risque de survenue
- Les mesures doivent être
  - Information du patient (Hygiène, diét)
  - Surveillance régulière multidisciplinaire (Med/paramed)
  - Traitement adapté
- La recherche doit se poursuivre
  - Quid de Mepitel ? Flammazine ?
  - innovation

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