Cellulitis risk factors for patients with primary or secondary lymphedema

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Table of Contents Summary

Cellulitis occurred in almost 40% of 1,846 patients with primary or secondary lymphedema of the upper or lower limb. Different risk factors for cellulitis were identified for primary and secondary lymphedema. Knowing cellulitis risk factors for the different lymphedema forms would help prevent this frequent complication, and enable practitioners to provide specific advice and adapt management.

Article Highlights

Type of Research: Single-center cross-sectional study

Key Findings: Based on 1,846 patients, different risk factors were identified according to the lymphedema form (primary or secondary, upper or lower limb). Awareness of those factors helps physicians recognize lymphedema promptly and refer patients to specialized centers to optimize management.

Take home Message: Awareness of risk factors for cellulitis in the different forms of lymphedema may contribute to preventing this frequent complication, and enable practitioners to provide specific advice and adapt management.

ABSTRACT

Background: Limb lymphedema is a chronic disease with primary and secondary forms, the latter essentially after cancer treatment.

Objectives: To analyze retrospectively cellulitis frequency and its associated risk factors in patients with primary or secondary limb lymphedema.

Methods: Information from all 1,991 patients referred to a specialized lymphedema center, from January to June 2018, was collected: previous cellulitis episode(s), clinical and lymphedema characteristics.

Results: Among the 1,846 patients whose information could be analyzed, 695 (37.6%) developed one or more cellulitis episodes and 23.3% had recurrent cellulitis. Cellulitis occurred in 39.5%, 30.5% or 38.6% ($P = .02$) of the patients with secondary upper limb, secondary lower limb or primary lower limb lymphedema, respectively; lymphedema had been present 106.5, 97 or 243.1 months. Lymphedema-onset-to-first-consultation (in our specialized center) interval, age at lymphedema onset and radiotherapy were independently associated with cellulitis but not axillary lymph-node excision, chemotherapy or lymphedema involvement. Lymphedema-onset-to-first-consultation interval and lymph-node excision were associated with cellulitis, while body mass index (BMI) or age at lymphedema onset for secondary lower limb lymphedema were not. For primary lower limb lymphedema, male sex, BMI and age at lymphedema onset were associated with cellulitis.

Conclusion: Different risk factors for cellulitis were identified for patients with lymphedema at risk. Awareness of those factors is important for physicians to recognize lymphedema promptly and refer patients to specialized centers to optimize management.

Keywords: Cellulitis; Frequency; Risk factors

INTRODUCTION

Lymphedema is a chronic, debilitating disorder responsible for enlargement of one or more limbs. Lymphedema is divided into primary and secondary forms, the latter essentially after cancer treatment. After breast cancer treatment including axillary lymph-node dissection, lymphedema occurs in almost one out of five women and 5.6% after sentinel lymph-node biopsy.¹ The main risk factors for developing upper limb lymphedema have been identified: axillary lymph-node dissection, radiotherapy, obesity [body mass index (BMI) >30 kg/m²], mastectomy and taxane chemotherapy.² For lower limb lymphedema, in industrialized countries, pelvic cancer (cervical, ovarian, uterine, prostatic) and melanoma are the main causes. Lymph-node excision combined with radiotherapy (external, brachytherapy) represents the main risk factor for lymphedema after cancer treatment.³

Primary lymphedema reflects a constitutional lymphatic system defect. It mainly affects young people, especially women, and is divided into non-syndromic forms: most frequently isolated lymphedema (including familial forms (ie, Milroy disease, related to vascular endothelial growth factor-receptor-3 (*VEGFR3*)-gene mutation) and syndromic forms, in which lymphedema is a clinical sign of a more complex syndrome, sometimes with a genetic origin, like Turner's syndrome.^{4,5} Primary lymphedema predominantly involves lower limb(s) and, very rarely, upper limb(s), genitals or the face.

For our team, cellulitis (erysipelas), caused by β -hemolytic streptococcus, is an acute dermohypodermatitis, ie, non-necrotizing cellulitis. Lymphedema is the most important risk factor for developing cellulitis.^{6,7} Indeed, Dupuy et al⁶ found lymphedema to be the strongest associated cellulitis risk factor (odds ratio (OR), 71.2), even preceding a break in the cutaneous barrier (leg ulcer, wound, fissurated toe-web intertrigo, pressure ulcer, leg dermatosis; OR, 23.8),

chronic venous insufficiency (OR, 2.9), leg edema (OR, 2.5) or overweight (BMI ≥ 25 and < 30 kg/m²) (OR, 2.0). No data are available about cellulitis in the different lymphedema forms.

The aim of our study was to determine cellulitis frequencies in patients with upper and/or lower limb primary or secondary lymphedema and to analyze the associated risk factors for cellulitis in each patient subgroup.

METHODS

Patients and methods. From January to June 2018, we collected data from all consecutive patients referred to our tertiary-care Department of Lymphology with a confirmed diagnosis of upper or lower limb lymphedema. Since 2006, our unit has been designated a member of the National Referral Centers for Rare Vascular Diseases dedicated to primary lymphedema. It also receives and treats patients with secondary post-cancer lymphedema. It oversees consultations and has a multidisciplinary team, trained in lymphedema management and comprised of physiotherapists, nurses, psychologist, podiatrists, dietician and an orthopedic specialist to obtain the detailed measurements needed to make the individually tailored elastic garments. Every month, our specialized lymphedema consultation team sees about 330 patients.

We recorded the following characteristics during the consultation: sex, age, age at first symptom, possible previous cancer and its treatment (surgery, lymph-node excision, chemotherapy, radiotherapy, hormone therapy), symptom-onset-to-specialized-consultation interval, lower-or-upper limb localization, limb involvement [complete: involving the entire limb; distal: below the knee (calf, foot) or the elbow (forearm, hand); proximal: involving the thigh, arm]; uni- or bilateral involvement; previous cellulitis (erysipelas) episode(s) (number), BMI (body weight (kg)/height²/m²)).

Unilateral limb lymphedema was diagnosed when the affected-limb circumference was 2-cm larger than that of the contralateral side. Lower limb lymphedema was confirmed clinically based on increased limb volume, with mandatory pathognomonic Stemmer's sign (inability to pinch the dorsal side of the skin of the second toe (or its base) confirming the diagnosis, except for the very rare proximal form (only affecting the thigh) which required magnetic resonance imaging or computed-tomography scan confirmation. Lower limb lymphoscintigraphy was obtained, when necessary, to confirm the diagnosis. Other diagnoses, such as lipedema, chronic venous insufficiency (regardless of clinical manifestations, etiological factors, anatomical distribution, and pathophysiological (Clinical, Etiological, Anatomical and Physiological (CEAP) stage)⁸ and various edema etiologies (cardiac, renal, hepatic) were excluded by physical examination and appropriate testing, such as venous ultrasonography, if necessary. None of the patients had previous venous or arterial ulcer(s), or had undergone surgical/endovascular venous treatment.

Cellulitis was defined as the association of systemic symptoms (fever ($>38^{\circ}\text{C}$) of sudden onset, chills) and local signs (erythema, pain, localized 'hot spot', increased volume) that required antibiotics. Cellulitis was diagnosed only when those criteria were met. Isolated redness on the lymphedematous limb without fever was not considered cellulitis. At each consultation, every 6 to 12 months, patients were asked if cellulitis satisfying those defined criteria had occurred during the interval since the last consultation. Moreover, at the first consultation, all patients had been taught to recognize the clinical signs of cellulitis to become his/her own expert. Recurrent cellulitis was defined as two or more episodes.

According to French law, Ethics Committee approval is not required because we conducted a retrospective and descriptive – not interventional – study, with patients managed according to our standard procedures and in respect of the Declaration of Helsinki. Informed written consent

for demographic, physiological and hospital-outcome data analyses was not obtained because this observational study did not modify existing diagnostic or therapeutic strategies. None of the patients was opposed to the use of their data.

Statistical analyses. Continuous variables are expressed as mean ($\pm$ standard deviation, SD) or median (interquartile range, IQR), and qualitative variables as number (%). Means were compared using Student's *t*-tests. Percentages were compared using χ^2 tests. Lymphedema characteristics were analyzed for their association with cellulitis in univariate and multivariate models, using backward stepwise logistic-regression analysis to identify and retain independent risk factors, respectively. Significance was defined as $P < .05$. All statistical analyses were computed using RStudio v1.0.136 software (RStudio, Inc, Boston, Mass, USA).

RESULTS

Information from 1,991 lymphedema patients was collected over the 6-month period, and 1,846 patients, divided into subgroups according to the lymphedema location (lower vs upper limb) and its form (primary vs secondary), were analyzed, as detailed in (Fig 1). Because primary upper limb lymphedema is very rare (only three patients with four-limb involvement and 27 (1.4%) primary upper limb lymphedemas were excluded from this analysis), and because secondary lymphedemas were exclusively post-cancer treatment, we analyzed three groups: post-breast cancer upper limb lymphedema ($n = 1062$), post-cancer lower limb lymphedema ($n = 325$) and primary lower limb lymphedema ($n = 459$). Patients and lymphedema characteristics for these three groups are reported in Table 1.

Among the 1,846 patients, 695 (37.6%) developed one or more cellulitis episodes and 23.2%

had recurrent cellulitis. Cellulitis occurred in 39.5%, 30.5% or 38.6% ($P = .02$) of the patients with secondary upper limb, secondary lower limb or, primary lower limb, respectively. Results of univariate analysis of risk factors for cellulitis in patients with primary or secondary lymphedema are given in Supplementary Tables.

Secondary upper limb lymphedema after breast cancer treatment. Among 1,692 women, 1,062 with upper limb lymphedema and mean BMI 27.8 kg/m^2 , mean lymphedema duration was 106.5 months. Among them, 39.5% previously had cellulitis, which was recurrent for 23.2%. Results of the multivariate analysis of risk factors for cellulitis in patients with secondary upper limb lymphedema are given Table 2. Lymphedema-onset-to-first-consultation interval (in our referral center), age at lymphedema onset and radiotherapy were independently associated with cellulitis while axillary lymph-node excision, chemotherapy or segmentation of the upper limb lymphedema were not.

Secondary lower limb lymphedema after cancer treatment. Three hundred and twenty-five patients with secondary lower limb lymphedema (82.2% female; mean BMI, 27.3 kg/m^2), most frequently after gynecological cancer treatment (49.8%), for a mean lymphedema duration of 97 months, were included. Among them, 30.5% had previous cellulitis episodes, which were recurrent for 21.2%. Multivariate analysis of these patients' risk factors for cellulitis are reported in Table 2. Lymphedema-onset-to-first-consultation interval and lymph-node excision were associated with cellulitis, while BMI or age at lymphedema onset were not.

Primary lower limb lymphedema. The 459 patients (79.1% female; mean BMI, 28.9 kg/m^2) had a mean age of 31.7 years at lymphedema (unilateral: 51.6%) onset. Among them, 38.6% had previous cellulitis episode(s), which were recurrent for 25.1%, with mean lymphedema duration of 243.1 months. Male sex, BMI and age at lymphedema onset were

associated with cellulitis (Table 3).

DISCUSSION

Herein, we reported that cellulitis occurred in 37.6% of the 1,846 patients with primary or secondary upper or lower limb lymphedema, whose lymphedema duration ranged from 97 to 243 months. Their recurrent cellulitis rate was 23.3%. Cellulitis was significantly associated with BMI, lymphedema-onset-to-first-consultation (in our specialized center) interval, age at lymphedema onset and radiotherapy for patients with secondary upper limb lymphedema after breast cancer treatment; lymphedema-onset-to-first-consultation interval and lymph-node excision for those with secondary lower limb lymphedema; and male sex, BMI and age at lymphedema onset for patients with primary lower limb lymphedema.

The precise cellulitis rate in a large series of patients with clinically diagnosed lymphedema, be it primary or secondary, or affecting upper or lower limbs, has not been analyzed previously. One major potential difficulty is the definition of cellulitis. At each consultation, every patient was asked whether cellulitis had occurred since the previous consultation. We considered a cellulitis diagnosis only when sudden fever onset was associated with localized signs (redness, increased volume of the lymphedematous limb, localized 'hot spot', pain). At the first consultation, every patient had been taught to recognize the clinical signs of cellulitis to become his/her own expert.

Mistry et al⁹ insisted that cellulitis was confirmed only in 31.9% of patients referred for suspicion of lower limb cellulitis in an English university center. Other diagnoses included venous eczema, chronic edema and lymphedema. Our cellulitis frequency confirmed previously reported findings for upper limb after breast cancer and lower limb lymphedema.¹⁰⁻¹³ In the

multicenter LIMPRINT study¹² from four countries (United Kingdom, France, Italy and Turkey), 32.2% of patients with primary lymphedema and 35.1% of those with secondary lymphedema had a history of cellulitis. Cellulitis frequencies in some studies^{14,15} were lower than herein, without any clearly discernable explanation, meaning that more than one-third of lymphedema patients developed one or more cellulitis episodes after lymphedema onset. Notably, bilateral lymphedema involvement did not increase the risk of lower limb cellulitis. Patients are prescribed measures to prevent cellulitis, such as meticulous skin care. Patients were instructed to avoid cutaneous abrasions (eg, cuts, burns, insect bites, cat scratches and cracks in dry skins) and to protect their skin during daily activities (using gloves for gardening, thimble when sewing, not walking barefoot). Patients were taught self-examination to search for toe-web intertrigo and its treatment.

Intriguingly, a long lymphedema-onset-to-first-consultation (in our specialized center) interval and young age at lymphedema onset were associated with cellulitis for secondary but not primary lymphedema. That is an important finding, with various consequences. Thus, for secondary lymphedema, especially of the upper limb after breast cancer treatment, oncologists, surgeons, radiotherapist need to be aware of this main complication so as to more rapidly refer the patient to a lymphedema specialist (physician, physiotherapist). Unfortunately, for primary lymphedema, the lymphedema-onset-to-first-consultation interval is often longer. Indeed, patients with primary lower limb lymphedema experienced longer delays between symptom onset and referral (14.0 vs. 3.5 years for secondary) in the study by Schallwani et al,¹⁴ which was confirmed in another study on only new patients referred to our center.¹³ Cellulitis occurrence could be a clinical factor heightening the awareness of other physicians of the need to consult a specialist in a referral center, which precipitated the initiation of lymphedema management.

Cellulitis was more frequent in patients with secondary than primary lymphedema, while the duration of follow-up was shorter. Those results suggest that underlying local immunological mechanisms may differ between secondary (acquired) and primary lymphedema. Notably, for 35 women with upper limb lymphedema after breast cancer treatment, cutaneous cell-mediated immunity, as assessed with dinitrochlorobenzene, was impaired.¹⁶ Lymphangiosarcoma (Stewart-Treves syndrome) may develop in a lymphedematous limb, essentially after breast cancer treatment, and only very rarely in primary lymphedema, suggesting an underlying immune deficiency,¹⁷ probably distinct for primary and secondary lymphedema. Further studies are required to explore immunological functions in patients with limb lymphedema, and comparisons of primary and secondary forms. Pertinently, decongestive physiotherapy is able to partially restore impaired cellular immune function (tuberculin skin test) in patients with upper limb lymphedema after breast cancer treatment.¹⁸ In their case-control study, Teerachaisakul et al¹⁹ found that the percentage circumference difference between the two limbs, primary lymphedema and systolic blood pressure were risk factors for cellulitis, and suggested that controlling lymphedema volume and systolic pressure might limit cellulitis frequency.

Based on this series, BMI was a risk factor only for primary lower limb lymphedema. That finding led us to hypothesize that fat-tissue deposition in the lower limb during lymphedema development might affect localized immunity, thereby facilitating infections. Obesity appears to be an independent risk factor for cellulitis. Precise effects on the immune response are poorly known. Adipose tissue is involved in inflammation and immunity, producing and secreting adipokines, either pro-inflammatory or anti-inflammatory, such as adiponectin or leptin.^{20,21} Moreover, fungal toe-web intertrigo is more common in obese than non-obese patients and represents a portal of entry for cellulitis.²² Moreover, obese patients' skin tends to be dry (with

the risk of cracks), associated with altered repair of the skin barrier. Lymphatic flow might also be damaged due to an inflammatory state.²³ Overweight and obese patients should have a specific consultation with a dietician or nutritionist to incite them to lose weight, even though weight loss seems to have little effect on lymphedema volume.²⁴ Hence, it is of interest to note that obesity is a proven risk factor for developing upper limb lymphedema after breast cancer treatment and its severity but not for favoring cellulitis once lymphedema is present.

Limitations. The main limitations of our study are its retrospective design, with the risk of patient-memory bias (age at lymphedema onset, cellulitis definition or confused with other dermatological diagnoses) and “survivor” bias, because we have the follow-up only for living patients, which might select only those with good prognoses. Another limitation is the absence of lymphedema-volume measurements, which is complicated for bilateral forms without a “normal” limb for comparison. The lack of information on dates of cellulitis occurrence precluded determining reliable frequency estimates. We did not include local risk factors, such as intertrigo, in this retrospective analysis because the site of entry of cellulitis may have disappeared by the time of the consultation during follow-up. None of the patients had present or previous limb wound(s) or ulcer(s). Lastly, we could not analyze the impact of compliance (compression, low-stretch bandage) as risk factor because cellulitis might modify lymphedema treatment and it is impossible to establish the temporal sequence.

CONCLUSION

Cellulitis is a frequent complication of primary and secondary lymphedemas of the upper or lower limb. Almost 40% of our patients had one or more cellulitis episode(s) with lymphedema duration ranging from 8 to 20 years among the different forms. Although different risk factors

were identified for primary and secondary lymphedema, lymphedema-onset-to-first-consultation interval (in our referral center), age at lymphedema onset and BMI appeared to be the most important associated with cellulitis. A major improvement would be shortening the interval between lymphedema onset and the first consultation in a specialized center to optimize and adapt lymphedema management to each patient, and hopefully limit complications, like cellulitis. Physicians, oncologists, surgeons and physiotherapists should be taught to recognize promptly lymphedema and so as to refer the patient to specialists in a timely manner.

Knowing the cellulitis risk factors for the different lymphedema forms may contribute to preventing this frequent complication, and enable practitioners to provide specific advice and adapt management.

Disclosures. Conflicts of interest: none.

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1 **Table 1.** Patient and lymphedema characteristics for the three lymphedema populations.

Characteristic	Upper limb after breast cancer treatment, n = 1062	Lower limb after cancer treatment, n = 325	Primary lower limb, n = 459
Sex, female	1062 (100)	267 (82.2)	363 (79.1)
Age at lymphedema onset, years	56.3 ± 11.8	56.6 ± 13.8	31.7 ± 18.6
Body mass index, kg/m ²	27.8 ± 6.1	27.3 ± 6.7	28.9 ± 7.7
Cancer			
Breast	1062 (100)	—	—
Gynecological ^a	—	162 (49.8)	—
Melanoma	—	65 (20)	—
Prostate	—	12 (3.7)	—
Other	—	86 (26.5)	—
Cancer treatment			
Surgery	1057 (99.5)	305 (93.8)	—
Tumorectomy	494 (46.5)	—	—
Mastectomy	558 (52.5)	—	—
Lymph-node excision	1019 (96)	242 (74.5)	—
Radiotherapy	984 (92.7)	184 (56.6)	—
Chemotherapy	877 (82.6)	140 (43.1)	—
Hormone therapy	579 (54.5)	15 (4.6)	—
Lymphedema-onset-to-1 st - consultation interval ^b , months	45.1 ± 69.7	52.7 ± 78.3	182.1 ± 187.6
Limb involvement			
Unilateral	1049 (98.8)	242 (74.5)	237 (51.6)
Proximal	104 (9.8)	52 (16)	6 (1.3)
Distal	158 (14.9)	52 (16)	269 (58.6)
Whole	800 (75.3)	221 (68)	184 (40.1)
Lymphedema duration, months	106.5 ± 95.7	97.0 ± 94.6	243.1 ± 198.8
Treatment			

Elastic compression	892 (84)	280 (86.2)	386 (84.1)
Low-stretch bandages	381 (35.9)	110 (33.8)	136 (29.6)
Manual lymph drainage	558 (52.5)	125 (38.5)	128 (27.9)
Past cellulitis	419 (39.5)	99 (30.5)	177 (38.6)
>2 times	246 (23.2)	69 (21.2)	115 (25.1)

Results are expressed as n (%) or mean $\pm$ SD.

^a Uterine, cervical, ovarian.

^b In our specialized center.

Table 2. Multivariate analysis of cellulitis risk factors for patients with secondary upper or lower limb lymphedema.

Factor	Odds ratio (95% CI)	<i>P</i> value
Upper limb lymphedema		
Body mass index, kg/m ²		.61
For each 1 kg/m ² increment	1.01 (0.98-1.03)	
For each 5 kg/m ² increment	1.03 (0.91-1.17)	
Lymphedema-onset-to-1 st -consultation interval ^a		<.0001
For each 1-month increment	1.007 (1.004-1.009)	
For each 12-month increment	1.08 (1.05-1.12)	
Age at lymphedema onset	0.98 (0.97-1.00)	.004
Radiotherapy	1.96 (1.01-4.0)	.05
Tumorectomy (vs. mastectomy)	1.26 (0.94-1.69)	.13
Unilateral side	0.62 (0.15-2.34)	.49
Hormonotherapy	0.78 (0.58-1.05)	.1
Diabetes	1.26 (0.64-2.45)	.51
Lower limb lymphedema		
Diabetes	0.42 (0.02-2.95)	.44
Body mass index (kg/m ²)	1.02 (0.97-1.08)	.46
Lymphedema-onset-to-1 st -consultation interval	1.006 (1.001-1.012)	.01
Unilateral lymphedema	0.64 (0.30-1.38)	.25
Lymph-node excision	3.50 (1.28-11.62)	.02
Chemotherapy	0.98 (0.50-1.90)	.95

Age at lymphedema onset

0.99 (0.96-1.01)

.25

1 ^a In our specialized center.

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Table 3. Multivariate analysis of cellulitis risk factors for patients with primary lower limb lymphedema.

Factor	Odds ratio (95% CI)	<i>P</i> value
Sex male	3.95 (2.15-7.46)	<.001
Body mass index (kg/m ²)	1.06 (1.02-1.09)	.002
Lymphedema-onset-to-1 st -consultation interval ^a	1.001 (0.999-1.002)	.33
Age at lymphedema onset	0.982 (0.967-0.999)	.04

^a In our specialized center.

1 **Figure legend**

2 **Figure 1.** Flow chart of the patients included in the study seen in consultation in our specialized
3 lymphedema-dedicated center from January to June 2018.

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Supplementary Tables. Univariate analysis of cellulitis risk factors for patients with secondary and primary lymphedema.

Primary lower limb lymphedema

Characteristic	OR (95% CI)	<i>P</i> value
Male sex	2.8 (1.77-4.46)	<10 ⁻³
Body mass index (kg/m ²)	1.05 (1.02-1.08)	.001
Lymphedema-onset-to-1 st -first consultation interval	1.002 (1.000-1.003)	.004
Age at lymphedema onset	0.986 (0.975-0.996)	.009
Diabetes	1.34 (0.38-4.50)	.64

Secondary upper limb lymphedema

Characteristic	OR (95% CI)	<i>P</i> value
Body mass index (kg/m ²)	1.000 (0.977-1.023)	.98
Diabetes	1.30 (0.71-2.36)	.38
Age at lymphedema onset	0.97 (0.96-0.99)	<10 ⁻⁵
Lymphedema-onset-to-1 st -first consultation interval	1.006 (1.004-1.008)	<10 ⁻⁵
Unilateral	0.29 (0.08-0.88)	.04
Hormonotherapy	0.76 (0.59-0.98)	.03
Radiotherapy	1.94 (1.16-3.35)	.01
Tumorectomy (vs mastectomy)	1.29 (1.01-1.66)	.04
Chemotherapy	0.88 (0.64-1.22)	.45
Lymph-node excision	1.18 (0.63-2.29)	.62

Secondary lower limb lymphedema

Characteristic	OR (95% CI)	<i>P</i> value
Diabetes	0.65 (0.09-2.73)	.59
Body mass index (kg/m ²)	1.02 (0.98-1.06)	.4
Lymphedema-onset-to-1 st -first consultation interval	1.005 (1.002-1.008)	.003
Chemotherapy	0.91 (0.55-1.49)	.71
Lymph-node excision	1.83 (0.89-4.05)	.11
Unilateral	0.95 (0.56-1.64)	.84
Age at lymphedema onset	0.97 (0.95-0.99)	.002
Male sex	1.25 (0.68-2.27)	.46
Radiotherapy	0.94 (0.57-1.56)	.8