

# Psychological effects of cetuximab-induced cutaneous rash in advanced colorectal cancer patients

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## Abstract

**Goals of work** Advanced colorectal cancer (CRC) has recently been treated with monoclonal antibodies, such as cetuximab. Skin toxicity is a peculiar side effect of cetuximab that may induce patients to interrupt therapy if it becomes serious. This study investigates the psychological and social sequelae of skin rash.

**Materials and methods** Patients affected by advanced CRC and treated with cetuximab-based therapy entered the trial. The following questionnaires were used: the Functional Assessment of Cancer Therapy—Colorectal (FACT-C) to measure quality of life (QoL) and the Psychological Distress Inventory (PDI). A single item regarding social avoidance was added with a three-point Likert scale.

Toxicity was assessed using the National Cancer Institute Criteria (NCI-2).

**Main results** Eighty patients were recruited; 41% presented psychological distress. As regards social avoidance, 53% of patients answered that they did not avoid going out at all. The rest of the sample answered that they “very much” (22%) or “somewhat” (25%) avoided going out. Psychological distress and social avoidance were not correlated to skin rash, but only to QoL.

**Conclusion** Skin rash was not found to impact patients' psychological status or social life. Two likely explanations for this finding were that (a) patients with advanced cancer consider skin rash as a part of the complex suffering caused by cancer and (b) patients are encouraged by oncologists to continue treatment because skin rash is indicative of response to therapy. This expectation brings hope and helps patients bear the drug-related side effects.

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The authors declare that the procedures followed were in accordance with the ethical standards of the Helsinki Declaration (1964, amended in 1975, 1983, 1989, 1996, and 2000) of the World Medical Association.

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**Keywords** Skin rash · Psychological distress · Cetuximab ·  
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## Introduction

Colorectal cancer (CRC) is one of the most common invasive cancers in western countries with 20% of patients initially diagnosed with locally advanced or metastatic disease [8]. In the last two decades, remarkable progress has been made in the treatment of metastatic disease following the introduction of oxaliplatin and irinotecan in the clinical practice. Both of these drugs, in combination with fluorouracil and folinic acid (Folfox and Folfiri regimens), obtain better response and survival rates [4, 21]. The development of biologic agents such as epidermal and vascular endothelial growth factor receptor

(EGFR and VEGFR, respectively) inhibitors seems to offer further therapeutic options. The monoclonal antibody cetuximab (Erbix<sup>®</sup>) is the most widely investigated EGFR inhibitor and it has been approved by the FDA for the treatment of patients with EGFR-expressing metastatic CRC.

Cetuximab treatment is associated with a peculiar skin toxicity with signs ranging from cutaneous rash to a papulopustular eruption that arises on the face and may spread to the upper torso and abdominal wall in serious cases. Skin toxicity may involve pruritus, it can badly deteriorate a person's physical appearance and thus cause treatment interruption [1, 2].

Most of the existing literature has stressed the psychological impact of changes in their body image for cancer patients, including hair loss [15] or mutilating surgical procedures such as mastectomy [17] or colectomy. Some physical signs, like alopecia or mastectomy, immediately recall cancer or cancer treatment, thus leading to the stigmatization of physical appearance rather than the illness itself. Given the lack of studies on the psychological impact of disfiguring cutaneous conditions in cancer patients, the extent to which skin rash may affect patients' psychological well-being remains unknown.

In a literature review by Sprangers et al. [18], the following dimensions were found to be significantly impaired in CRC patients: physical functioning (e.g., constipation or diarrhea), social functioning (e.g., going out), and sexual functioning both for men and women.

It has also been reported that the availability of emotional and instrumental support has an impact on quality of life (QoL) of cancer patients [19].

While different studies have investigated [7] the activity and efficacy of cetuximab-based therapies in the treatment of advanced CRC patients, little information concerning QoL in this population is currently available and results regarding QoL over time and its relationship to survival are inconsistent [6]. QoL assessments can indeed help to discriminate between competing treatments that may achieve similar biological outcomes. Hence, more research has been required [20] to shed light on the impact of these therapies on health-related QoL, since most of the studies have failed to report QoL data.

The primary endpoint of the present study was to investigate the relationship between skin rash and psychological distress and to assess whether these conditions can lead to avoidance of social contacts, which is sometimes the case for patients with alopecia [10].

The second aim of this research was to evaluate the overall QoL in advanced CRC patients treated with cetuximab while controlling for associated chemotherapy regimens.

## Materials and methods

Ethical approval for this study was obtained from the Ethical Committees of the Cancer Centres in Southern Italy involved in the study.

All consecutive patients with advanced CRC and treated with cetuximab-based therapy from June 2006 to October 2007 entered the trial. Inclusion criteria were the following: (a) aged 18–75 years, (b) performance status (ECOG, 0–2), (c) written informed consent to participate in the study, and (d) fluency in Italian. A minimum of four cycles of chemotherapy were to be administered to patients entering the trial.

Cancer patients were recruited by trained clinical psychologists. All of the patients were assessed through the following scales administered in Italian:

1. The Functional Assessment of Cancer Therapy—Colorectal (FACT-C; Appendix 1) was used to investigate QoL. This questionnaire is part of the Functional Assessment of Chronic Illness Therapy Measurement System, which comprehensively assesses the health-related QoL of cancer patients. It is composed of 27 items from the general version of the Functional Assessment of Cancer Therapy (FACT-G) constituting a general core QoL measure with the following domains: physical well-being, social/family well-being, emotional well-being, and functional well-being. It has a disease-specific subscale containing nine specific CRC items [3, 24].
2. The Psychological Distress Inventory (PDI; Appendix 2) is a self-administered 13-item questionnaire measuring psychological distress in cancer patients during the week prior to its administration. PDI is a reliable and effective tool for measuring psychological distress in cancer patients and detecting psychiatric disorders through a screening procedure [13]. Answers are measured on a five-point Likert scale.
3. Social avoidance was measured using a single item “I avoid going out or seeing persons because of my skin toxicity,” measured on a three-point Likert scale.
4. Toxicity was assessed through the National Cancer Institute Criteria (NCI-2).

Descriptive statistics have been used to summarize demographic and study variables. The significance of correlations between study variables was assessed by the chi-square test, Pearson's correlation coefficient, and Spearman's test, as specified in the results. The *t* test was used to compare the mean values of continuous variables, both for PDI and FACT-C. A *p* value <0.05 was considered statistically significant. All analyses were performed using SPSS for Windows, version 13.0.

## Results

A total of 80 patients were enrolled in the study; their characteristics are shown in Table 1.

### Psychological distress

Forty-one percent of the patients showed psychological distress (assuming 29 as the cutoff for high sensitivity and specificity for the Italian sample) [13], while 55% were not distressed (Table 2). A *t* test was carried out to compare the mean values between our study population (mean=30.09, standard deviation [SD]=9.33) and the population of the PDI validation study (mean=30.9, SD=9.69). No significant differences were found between the two samples ( $p=0.583$ ).

No correlation was found between skin rash and psychological distress (chi-square,  $p=0.410$ ) even after controlling for patient's gender. A significant correlation was found between psychological distress and overall QoL (Pearson's correlation coefficient= $-0.67$ ,  $p<0.0001$ ; Table 3).

### Social avoidance

Fifty-three percent of the patients answered that they did “not at all” avoid going out (Table 4). The remaining half of the sample answered that they “very much” (22%) or “somewhat” (25%) avoid going out. Social avoidance was not found to correlate with skin rash as had been initially anticipated (chi-square,  $p=0.469$ ; Spearman's rho,  $p=-0.138$ ) even after controlling for gender. It was found to correlate only with QoL (chi-square= $0.443$ ,  $p<0.000$ ).

### Health-related quality of life

The mean values and SDs for the population studied are listed in Table 5. In order to evaluate the QoL of the present

**Table 1** Sample characteristics

Sample characteristics, $n=80$	
Sex	57% men, 43% women
Age	33–74 years old (mean=59)
Cancer site	100% advanced CRC
Cutaneous rash	No rash, 9%; G1, 45%; G2, 28%; G3, 15%; G4, none (missing 3%)
Chemotherapy	37% irinotecan-based; 47% oxaliplatin-based; 2% bevacizumab; 10% cetuximab monochemotherapy (missing 4%)
Institution	80% National Cancer Institute “Giovanni Paolo II”, Bari; 20% IRCCS “Casa Sollievo della Sofferenza”, San Giovanni Rotondo

**Table 2** Percentages of psychological distress

Psychological distress	Mean=30.09	Number (percent)
Distress (PDI >29)	38.71	33 (41)
No distress	23.67	44 (55)
Missing	–	3 (4)

sample, the data were compared with the validation study of test FACT-C carried out by Yoo et al. in 2004 [26] on a population of patients who received colectomy and were partly treated with adjuvant chemotherapy. The *t* test was carried out to compare mean values and the results showed that the physical ( $p=0.009$ ), emotional ( $p=0.000$ ), and functional ( $p=0.000$ ) dimensions were significantly worse in our sample, but the specific colorectal symptoms subscale scored better than in the study sample of Yoo et al. ( $p=0.000$ ). No differences in social well-being were observed between the two populations.

Analysis of variance was carried out to compare mean values of the QoL domains between the two main chemotherapy groups, namely, cetuximab + irinotecan and cetuximab + oxaliplatin. No significant difference was found between the two groups.

The weight of the single FACT-C subscales (physical, social/familiar, emotional, functional, additional concerns) on PDI was measured to understand which factor was more strongly correlated with PDI. All the subscales proved to be significantly correlated with PDI (Table 6) with the physical subscale's correlation being the strongest.

## Discussion

To our knowledge, this is the first quantitative study on the psychological sequelae of cetuximab-induced acneiform rash in CRC patients.

Forty-one percent of the patients in this sample were psychologically distressed. The presence of mood disorders in cancer is reported to range from 30% to 50% of patients in the literature [14]; so, our sample showed mild psychological distress.

Previous studies had found that many patients with advanced cancer—who constitute the totality of our

**Table 3** Correlations among study variables

	QoL ( $p$ value)	Skin rash ( $p$ value)
Psychological distress	<0.0001 (Pearson's correlation coefficient)	0.410 (chi-square test)
Social avoidance	<0.000 (chi-square test)	0.469 (chi-square test)

**Table 4** Incidence of social avoidance

I avoid going out or seeing persons because of my skin toxicity	Number (percent)
Not at all	42 (53)
Somewhat	20 (25)
Very much	18 (22)

study sample—do not consider themselves to be suffering [25]. This may depend on a better adaptation to illness-related strains since, with advanced illness, patients and families are faced with more concerns regarding survival and physical symptoms on the one hand while in the meantime they learn to better cope with illness, disabilities, and changing roles. Additional resources are thus available to help them come to terms with the situation.

With regard to the first hypothesis of this study, i.e., that there may be a correlation between skin rash and psychological distress, our results provided no confirmation of such a relationship. In this study sample, skin rash did not negatively impact cancer patients' psychological status, and this was true for both men and women.

In a previous study on the psychological impact of disfiguring conditions, patients' levels of psychosocial distress were not found to be properly predicted by the severity of disfigurement [16]. Moreover, as pointed out previously, patients with a longer history of cancer disease are often already compromised in their physical appearance and consider skin rash to be only part of the complex suffering of coping with advanced cancer.

When openly talking to patients about cetuximab, a further explanation for this emerges which regards hopes and expectations: patients are encouraged by oncologists to continue treatment because skin rash is indicative of response to therapy [5]. Hence a “frame effect” [22] may take place: the reframing of an illness-related experience (skin rash) in a positive frame (a better response to treatment) helps patients perceive and adapt to the negative event differently. Moreover, hope has been identified as an essential resource in the lives of people with cancer, helping them to cope with suffering and uncertainty [12]. This

expected relation between rash and treatment efficacy brings patients to find a meaning in therapy-induced side effects. Personal meaning is related to lower psychological distress because of the heightened sense of control on a traumatic event [11].

In terms of expectations, a social variable needs to be taken into account: the pharmaceutical companies' use of media has brought new attention to the importance of biologic treatments for CRC, emphasizing their efficacy and few side effects. This may enhance patients' expectations about the benefits of such therapies, thus overriding their concerns about side effects, including skin toxicity.

The other study point was the issue of social avoidance, namely, whether patients with skin rash avoided social situations because of it. Our findings are in contrast with a previous qualitative study on cetuximab-induced acne [23] where a considerable proportion of patients experienced psychosocial difficulties and social avoidance. Half of our sample did not avoid social activities at all, whereas the remaining half did partly avoid social contacts, but this was not related to rash. In our sample, social avoidance was mostly correlated to patients' overall QoL and this was in agreement with various studies regarding patients with disfigured facial esthetics [9]. A limitation of this finding is that the specificity and sensitivity of the single item on social avoidance was not previously validated as a measure to assess this topic.

The other research point we investigated was overall QoL, specifically for CRC patients. A significant correlation was found between patients' psychological distress and overall QoL. Patients with cancer are more distressed by a cluster of symptoms than by a single one, which can be easily accepted when it is part of a treatment perceived as life-sparing. Our sample showed a lower QoL in all FACT-C dimensions compared to the validation study of Yoo et al. [26], with the exception of the subscale of CRC symptoms (e.g., diarrhea, reduction of appetite, loss of weight). The main explanation for this finding is that the population sample in that study was made up of patients who had undergone colectomy and 76% of them had received adjuvant chemotherapy after the first cancer diagnosis, whereas our sample was made up of patients with advanced stages of disease, some of them treated with

**Table 5** Mean values of FACT-C

FACT-C subscales	Study sample, median (SD)	Yoo et al., median (SD)	<i>t</i> test ( <i>p</i> value)
Physical well-being	19.85 (5.53)	22.62 (5.91)	0.009
Social well-being	15.58 (4.93)	15.38 (5.92)	No significance
Emotional well-being	14.35 (4.31)	19.28 (4.65)	0.000
Functional well-being	10.89 (5.96)	16.90 (6.82)	0.000
CRC symptoms	20.09 (5.81)	16.66 (4.77)	0.000
General well-being	80.02 (19.52)	90.84 (20.71)	0.004

**Table 6** Spearman's rho correlation of PDI with FACT-C subscales

FACT-C	Physical well-being	Familiar/social well-being	Emotional well-being	Functional well-being	Additional concerns	General well-being
PDI	-0.627**	-0.435**	-0.539**	-0.530**	-0.362**	-0.678**

\*\* $p \leq 0.01$

multiple chemotherapy lines and thus more physically distressed. Of course, QoL comprises various factors, including physical well-being, which contributed to the whole definition and evaluation of QoL. Actually, another limitation of this study is that rash-related symptoms, namely, pruritus or skin dryness, were not measured with a specific questionnaire or specific items and patients may have referred to such problems when answering some of the FACT-C physical well-being items. Thus, the load of rash-related physical problems was not specifically addressed. Specific tools to measure skin rash should be developed or adapted for EGFR inhibitor-related side effects in cancer patients.

In conclusion, this is the first quantitative study on the psychological consequences of cetuximab-induced cutaneous rash in CRC patients, demonstrating no correlation between skin rash and psychological distress or social avoidance while pointing to a strong correlation that was found between QoL and psychological distress or social avoidance.

Further studies will clarify the role of interdependent physical and psychological domains in the well-being of advanced CRC patients, with a particular focus on physical appearance, adaptation to the illness, meaning finding, and QoL.

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## Appendix 1

The FACT-C (Version 4)

### PHYSICAL WELL-BEING

I have a lack of energy.

I have nausea.

Because of my physical condition, I have trouble meeting the needs of my family.

I have pain.

I am bothered by side effects of treatment.

I feel ill.

I am forced to spend time in bed.

### SOCIAL/FAMILY WELL-BEING

I feel close to my friends.

I get emotional support from my family.

I get support from my friends.

My family has accepted my illness.

I am satisfied with family communication about my illness.

I feel close to my partner (or the person who is my main support).

I am satisfied with my sex life.

### EMOTIONAL WELL-BEING

I feel sad.

I am satisfied with how I am coping with my illness.

I am losing hope in the fight against my illness.

I feel nervous.

I worry about dying.

I worry that my condition will get worse.

### FUNCTIONAL WELL-BEING

I am able to work (include work at home).

My work (include work at home) is fulfilling.

I am able to enjoy life.

I have accepted my illness.

I am sleeping well.

I am enjoying the things I usually do for fun.

I am content with the quality of my life right now.

### ADDITIONAL CONCERNS

I have swelling or cramps in my stomach area.

I am losing weight.

I have control of my bowels.

I can digest my food well.

I have diarrhea.

I have a good appetite.

I like the appearance of my body.

Do you have an ostomy appliance?

*If yes, please answer the next two items:*

I am embarrassed by my ostomy appliance.

Caring for my ostomy appliance is difficult.

ANSWERS: (0) not at all; (1) a little bit; (2) somewhat; (3) quite a bit; (4) very much.

## Appendix 2

The Psychological Distress Inventory (PDI)

In the last week:

1. Do you think your desire to speak with others has diminished?
2. Have you felt calm?



3. Have you experienced moments of anxiety or inner tension?
4. Have you felt tired or lacking in energy?
5. Have you felt more alone?
6. Have you felt better?
7. Have you experienced moments of dejection or depression?
8. Do you think that your illness might have created problems of self-image for you that did not exist before?
9. Have you felt worthless?
10. Have you felt a lack of willpower?
11. Has your interest in the world that surrounds you diminished?
12. Have you felt that your sexual desire has diminished?
13. Has your illness negatively influenced your relationship with others?

ANSWERS: (1) not at all; (2) a little; (3) quite a bit; (4) much; (5) very much.

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