A prospective analysis of factors that influence weight loss in patients undergoing radiotherapy

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Abstract

Malnutrition occurs frequently in patients with cancer. Indeed, a variety of nutritional and tumor-related factors must be taken into account in these patients. Recognizing this relationship, we aimed to prospectively evaluate the risk factors that influence weight loss in patients undergoing radiotherapy with oral nutritional supplementation and dietetic counseling. Weight loss of 74 patients during radiotherapy and 1 month after treatment was analyzed. Parameters such as age, gender, tumor location, tumor stage, Eastern Cooperative Oncology Group performance status (ECOG PS) score, and the use of chemotherapy were analyzed to evaluate their influence on weight loss. All patients underwent oral nutritional supplementation and dietetic counseling. Forty-six (65.7%) patients lost weight, with a mean weight loss of (4.73 ± 3.91) kg, during radiotherapy. At 1 month after treatment, 45 (66.2%) patients lost weight, presenting a mean weight loss of (4.96 ± 4.04) kg, corresponding to a (6.84 ± 5.24)% net reduction from their baseline weight. Head and neck cancer patients had a mean weight loss of (3.25 ± 5.30) kg, whereas the remaining patients had a mean weight loss of (0.64 ± 2.39) kg (P = 0.028) during radiotherapy. In the multivariate analysis, the head and neck tumor location (P = 0.005), use of chemotherapy (P = 0.011), and ECOG PS score of 2–3 (P = 0.026) were considered independent risk factors. Nutritional status and parameters, such as tumor location (especially the head and neck), the use of chemotherapy, and the ECOG PS score, should be evaluated before radiotherapy because these factors can influence weight loss during radiotherapy and 1 month after treatment.

Key words  Nutrition, radiotherapy, weight loss, oral nutrition supplementation

Materials and Methods

Study design

This study was approved by the Cruces University Hospital.
Nutritional support in patients undergoing radiotherapy

Jon Cacicedo et al.

Ethics Committee. According to the Spanish Nutrition and Cancer Group[9,10] and the European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines[11], nutritional therapy should be initiated if malnutrition already exists or if it is anticipated that the patient will be unable to eat for more than 7 days. Enteral nutrition should also be initiated if an inadequate food intake (<60% of estimated energy expenditure) is anticipated for more than 10 days[11]. The ESPEN guidelines also recommend using intensive dietary advice and oral nutritional supplementation during radiotherapy of the head and neck region. Thus, patients with at least a 5% weight loss (any tumor location) prior to radiation were considered eligible regardless of whether the proposed radiotherapy was primary, adjuvant to surgery, combined with chemotherapy, or with palliative intent. Patients with head and neck carcinoma with or without previous weight loss were also eligible.

Patients were recruited between August 2011 and February 2012. Informed consent was obtained from each patient prior to inclusion. The patients were treated with continuous, once-daily radiation delivered 5 days per week. All patients underwent oral nutrition supplementation and dietetic counseling as supportive care. No control group was included for ethical reasons[11,12].

Nutritional considerations

All patients were given general dietary recommendations for specific cancers and according to therapy type. In general, we recommended a balanced and healthy diet according to their symptoms, such as anorexia, nausea, dysphagia, and mucositis, to facilitate appropriate calory intake. Dietary recommendations were adjusted to control tumor-associated symptoms or treatment toxicity. Patients were encouraged to gradually introduce semisolid and liquid foods, depending on the degree of dysphagia. If needed, patients were instructed to reduce the amount of food consumed for each meal while increasing the daily number of meals. Patients began treatment with both dietetic counseling and supplements. The supplements used were liquid multinutrient supplements containing sources of energy, protein, and a range of micronutrients. Each 200 mL can of formula provides 18.8 g protein and 250 kcal. The formulas were enriched with omega-3 fatty acids. A uniform amount of supplement was provided (2 cans per day). Patients were instructed to use the supplements as drinks in addition to their usual diet. We expected the oral nutrition supplements to contribute a supplementary intake of up to 500 kcal/day in addition to the normal diet. All patients were encouraged to continue the oral nutritional supplementation for at least 1 month after treatment. All patients affirmed that they were consuming the prescribed supplementation based on a consumption record (yes/no) that was checked weekly during radiotherapy. However, we found it difficult to evaluate the precise quantity in milliliters that was consumed by each patient. Thus, we did not perform this additional analysis in this setting.

Nutritional assessment

Data were collected for all patients at the first clinical visit, including the patient’s age, gender, tumor stage, primary diagnosis, chemotherapy protocol, and ECOG PS score. The baseline body weight was defined as the weight at the time of the initial consultation. Nutritional assessment (body weight and dietetic counseling) was performed before treatment. Initial nutritional measures included the baseline weight and self-reported weight loss within 6 months preceding the first clinical visit. A blood count including the serum albumin level was obtained before treatment and at the end of radiotherapy. The installation of a nasogastric tube or gastrostomy to provide enteral nutrition during treatment was performed when the oral consumption of food was no longer sufficient to maintain the patient’s weight or when aspiration was detected. Gastrostomy was employed when the patient refused a nasogastric tube. No prophylactic feeding tube was employed. Toxicity was reported according to the Common Terminology Criteria for Adverse Events (CTCAE v. 4.0). Weight loss was evaluated weekly during radiotherapy and 1 month after treatment.

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation (SD). Categorical variables are described as numbers and percentages. Student t-test and the Mann-Whitney U-test were used to compare the weight loss during radiotherapy and 1 month after treatment with the following variables: age, gender, tumor location, tumor stage, ECOG PS score, and the use of chemotherapy. The weight loss during radiotherapy was calculated as the difference between the weight at the start and the end of radiotherapy. The weight loss at 1 month after treatment was calculated as the difference between the weight at the start and 1 month after radiotherapy. Linear univariate regression analysis was performed to evaluate the associations of the previously indicated variables with weight loss. Variables with a P < 0.200 in the univariate analysis were included in the multivariate stepwise non-automatic model. We eliminated the variable with the highest P value and repeated the model; this procedure was repeated until all variables were found to be significant.

Statistical significance was defined by a P value less than 0.05. Data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 19.0).

Results

Characteristics of the patients

A total of 74 patients, including 63 (79.8%) men and 11 (20.2%) women with a median age of 60 years (range, 39–85), were recruited; 24 patients (36.7%) were older than 65 years of age, and 50 (63.3%) were ≤ 65 years of age. The tumor locations and radiation doses are shown in Table 1.

Weight loss during radiotherapy and one month after treatment

During radiotherapy, 46 (65.7%) patients lost weight, with a mean weight loss of (4.73 ± 3.91) kg, which corresponded to a (6.55 ±
4.84%) net reduction from their baseline weights. One month after treatment, 45 (66.2%) patients lost weight, with a mean weight loss of (4.96 ± 4.04) kg, which corresponded to a (6.84 ± 5.24)% net reduction from their baseline weights. For this group of 74 patients, the average net weight loss was 2.35 kg during radiotherapy and 2.17 kg at 1 month after treatment. The trend of weight loss during radiotherapy is shown in Figure 1.

**Relationship between weight loss and clinical parameters**

As shown in Table 2, weight loss was associated with tumor location, tumor stage, and toxicity (all P < 0.05), but showed no relationships with the patient's age, gender, ECOG PS score, the use of chemotherapy, and feeding tube placement (all P > 0.05).

The mean weight loss was significantly higher for patients with head and neck tumors than for patients with tumors at other locations either during radiotherapy (P = 0.028) or 1 month after treatment (P = 0.034).

The mean weight loss was significantly lower for patients in stages I–II than for patients in stages III–IV either during radiotherapy (P = 0.005) or 1 month after treatment (P = 0.022). In a subanalysis for patients with head and neck tumors, the mean weight loss also showed strong relationship with tumor stage (both P < 0.05).

The influence of toxicities on weight loss was analyzed only for patients with head and neck tumors; no patient with a tumor in another location developed adverse events above grade II. The mean weight loss during radiotherapy was significantly lower for patients with grade I–II mucositis than for those with grade III mucositis (P = 0.009), no significant difference in weight loss between these two

### Table 1. Distribution of tumor location and radiation dose of the 74 patients

| Tumor location | Number (%) of patients | Mean dose (Gy) | Number (%) of patients who underwent chemotherapy |
|----------------|------------------------|----------------|-----------------------------------------------|
| Head and neck  | 50 (67.6)              | 66.7 (30.0–72.5) | 32 (64.0)                                    |
| Brain          | 1 (1.4)                | 60.0           | 1 (100)                                      |
| Rectum         | 3 (4.1)                | 45.0           | 3 (100)                                      |
| Lymphoma       | 1 (1.4)                | 50.0           | 1 (100)                                      |
| Breast         | 1 (1.4)                | 60.0           | 1 (100)                                      |
| Lung           | 14 (18.9)              | 58.2 (37.8–66.0)| 11 (78.6)                                   |
| Esophagus      | 3 (4.1)                | 51.3 (50.0–54.0)| 2 (66.7)                                    |
| Stomach        | 1 (1.4)                | 45.0           | 1 (100)                                      |
| Total          | 74 (100)               | NA             | 52 (70.2)                                    |

NA, not applicable.

Figure 1. Weight loss of the 74 patients during radiotherapy. The weight of each patient was measured weekly during radiotherapy and 1 month after treatment. The mean weight of the 74 patients decreases during radiotherapy. W1–8, from the first to the eighth week of radiotherapy; M1: one month after treatment.
groups was found 1 month after treatment (P > 0.5).

At the beginning of radiotherapy, the mean body mass index (BMI) was 26.62. The mean BMI at the end of radiotherapy was 24.64. Although BMI clearly decreased during radiotherapy, as expected, there was no significant association between BMI and toxicity.

**Regression analysis of clinical parameters affecting weight loss during and after radiotherapy**

The patient’s age, gender, ECOG PS score, tumor location, tumor stage, and the use of chemotherapy were included in the regression analysis. The multivariate analysis showed that the head and neck tumor location (P = 0.005) and the use of chemotherapy (P = 0.011) were independent risk factors of weight loss during radiotherapy, whereas an ECOG PS score of 2–3 (P = 0.026) and the use of chemotherapy (P = 0.009) were independent risk factors of weight loss at 1 month after treatment. The statistical data from both univariate and multivariate analyses are presented in Table 3.

**Discussion**

Risk factors such as the head and neck tumor location, the use of chemotherapy, and an ECOG PS score of 2–3 should be evaluated because they can influence weight loss during radiotherapy and 1 month after treatment. Our findings further support the importance of weight control in patients undergoing radiotherapy. Other authors have reported similar results\[13\].

Currently, oral nutritional supplementation is recommended in patients with malnutrition, using a formula adapted to the patient’s particular needs\[8\]. Ravasco et al.\[14,15\] have demonstrated the effectiveness of dietetic counseling in patients with head and neck cancer. They reported greater improvement in the quality of life of patients with head and neck cancer who received counseling compared with those who received only supplements without any advice. Ravasco et al.\[16\] have also demonstrated that dietetic counseling is as effective as a high-energy, high-protein oral nutritional supplementation in colorectal cancer patients undergoing radiotherapy. In addition, a systematic review performed by Elia et al.\[17\] have shown that liquid multinutrient oral nutritional supplementation significantly increased the total energy intake compared with routine care in patients undergoing radiotherapy. Taking into account the conclusions of these studies, it was considered that the best nutritional strategy for the patients in this study was to use dietetic counseling and oral nutritional supplementation to increase dietary intake and prevent therapy-

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**Table 2. The relationships between weight loss and clinical parameters of the 74 patients**

| Clinical parameter                        | No. of patients | Weight loss (kg) | P     | Weight loss (kg) | P     |
|------------------------------------------|----------------|-----------------|-------|-----------------|-------|
|                                         |                | During radiotherapy |      | One month after radiotherapy |      |
| Age (years)                             |                |                  | 0.199 |                 | 0.489 |
| > 65                                     | 24             | 1.63 ± 3.88      |       | 1.27 ± 3.34     |       |
| ≤ 65                                     | 50             | 2.48 ± 5.99      |       | 2.82 ± 5.29     |       |
| Sex                                      |                |                  | 0.371 |                 | 0.865 |
| Men                                      | 63             | 2.62 ± 4.98      |       | 1.39 ± 3.24     |       |
| Women                                    | 11             | 2.23 ± 5.39      |       | 1.97 ± 4.77     |       |
| Tumor location                           |                |                  | 0.028 |                 | 0.034 |
| Head and neck                           | 50             | 3.25 ± 5.30      |       | 3.02 ± 5.79     |       |
| Others                                   | 24             | 0.64 ± 2.39      |       | 0.53 ± 3.43     |       |
| Tumor stage\[a\]                        |                |                  | 0.005 |                 | 0.222 |
| I–II                                     | 13             | 0.94 ± 3.03      |       | 1.06 ± 3.91     |       |
| III–IV                                   | 58             | 3.01 ± 4.71      |       | 2.76 ± 5.15     |       |
| Tumor stage for patients with HN tumors |                |                  | 0.006 |                 | 0.027 |
| I–II                                     | 14             | 0.77 ± 3.20      |       | 1.04 ± 4.47     |       |
| III–IV                                   | 36             | 4.07 ± 5.27      |       | 3.81 ± 5.61     |       |
| ECOG PS score\[b\]                      |                |                  | 0.274 |                 | 0.090 |
| 0–1                                      | 59             | 2.47 ± 4.61      |       | 2.22 ± 5.40     |       |
| 2–3                                      | 5              | 5.23 ± 7.61      |       | 6.54 ± 6.88     |       |
| Chemotherapy                             |                |                  | 0.068 |                 | 0.069 |
| Yes                                      | 52             | 3.11 ± 4.90      |       | 3.07 ± 5.38     |       |
| No                                       | 22             | 0.60 ± 3.49      |       | 0.43 ± 4.50     |       |
| Toxicity in patients with HN tumors     |                |                  | 0.009 |                 | 0.118 |
| Grade I–II mucositis                     | 29             | 1.55 ± 4.60      |       | 2.44 ± 5.41     |       |
| Grade III mucositis                      | 21             | 6.51 ± 5.78      |       | 5.01 ± 6.69     |       |

HN, head and neck; ECOG PS, Eastern Cooperative Oncology Group performance status. \[a\] The staging information of 3 patients (4.1%) is unavailable. \[b\] The ECOG PS scores of 10 patients (13.5%) are unavailable.
associated weight loss. All patients in the present study were considered candidates for oral nutritional supplementation; once an individual is identified to have malnutrition or presents with high risk of malnutrition, it would be ethically inappropriate to withhold nutritional support.

The influence of tumor location on weight loss was analyzed. Patients with head and neck tumors clearly lost more weight (at least 5 times more) both during radiotherapy and at 1 month after treatment compared with patients with other tumor locations, which stresses the major role of tumor location, as previously reported\cite{3,18,19}. The head and neck tumor location influenced weight loss during radiotherapy and was considered significant in multivariate analysis. Our results highlight the importance of considering patients with head and neck tumors as high risk, and nutritional assessment and oral nutritional supplementation should play an essential role during radiotherapy in this group\cite{9,11-13}. Patients with head and neck tumors have complex nutritional problems due to both tumor-related and treatment-induced symptoms. Indeed, the relationship between weight loss and survival has been previously reported\cite{19}. According to our results, patients with head and neck tumors who experienced grade III mucositis and who were classified as having advanced cancer lost more weight than patients with grade I–II mucositis and patients with early-stage cancer (I–II). In addition, Valentini et al.\cite{20} have recently reported that the frequency of grade III mucositis was higher in patients in whom weight loss during radiotherapy was more pronounced. Thus, weight loss may be substantial in patients with advanced cancer and when patients present with higher grade toxicity. In fact, Mangar et al.\cite{13} have reported that advanced tumor stage should be used to identify patients who are at high risk of malnutrition during radiotherapy. Hence, special attention should be paid to these cases.

In the present study, patients who underwent chemotherapy (concomitant chemotherapy in 90.2% of these patients) had a significant weight loss during radiotherapy and even greater weight loss 1 month after treatment compared with patients who did not undergo chemotherapy. This observation led us to consider chemotherapy a major risk factor influencing weight loss. It is known that the use of chemoradiotherapy produces a radiosensitization effect that leads to increased acute toxicity. The fact that the patients who underwent chemotherapy lost more weight further substantiates that chemoradiotherapy can be intensive and can be associated with severe acute toxicity, especially in patients with head and neck tumors. This fact, as well as nausea and vomiting, may contribute to increasing weight loss in patients undergoing radiotherapy\cite{13,21}. Currently, there is a lack of evidence-based data regarding toxicities in elderly patients, especially in the field of radiotherapy\cite{22}. In our study, weight loss showed no significant association with age. However, other authors have reported opposite results\cite{13}. The lack of significant association is likely due to the small percentage (36.7%) of patients studied over 65 years, which makes it difficult to find a significant age-related difference.

In our study, there was little need for feeding tube placement. The installation of a nasogastric tube or gastrostomy was performed only when the oral consumption of food was no longer sufficient to maintain a patient’s weight or when aspiration was detected. No prophylactic feeding tube was employed. Only 10.9% of the patients required a feeding tube, which is considered low compared with the results from other studies\cite{5,23} and especially considering that 67.6% of the patients in this study had head and neck tumors.

| Variate                      | Univariate | Multivariate |
|------------------------------|------------|--------------|
|                              | β          | P            | β             | P          |
| Weight loss during radiotherapy |            |              |               |            |
| Age                          | -1.557     | 0.199        | 3.239         | 0.005      |
| Gender                       | -1.227     | 0.371        |               |            |
| HN tumor location            | 2.604      | 0.026        | 3.239         | 0.005      |
| ECOG PS 2–3                  | 2.752      | 0.274        | 3.239         | 0.005      |
| Tumor stage                  | 3.963      | 0.005        | 3.239         | 0.005      |
| Chemotherapy                 | 2.510      | 0.046        | 3.239         | 0.005      |
| Weight loss one month after treatment |            |              |               |            |
| Age                          | -0.848     | 0.537        | 5.229         | 0.026      |
| Gender                       | -0.263     | 0.865        | 5.229         | 0.026      |
| HN tumor location            | 2.490      | 0.063        | 5.229         | 0.026      |
| ECOG PS 2–3                  | 4.325      | 0.090        | 5.229         | 0.026      |
| Tumor stage                  | 3.829      | 0.015        | 5.229         | 0.026      |
| Chemotherapy                 | 2.650      | 0.054        | 5.229         | 0.026      |

Abbreviations as in Table 2.
optimal method of enteral nutrition remains a matter of debate. Tube feeding can be delivered via either a nasogastric feeding tube or a gastrostomy. Chen et al. have shown that the placement of a prophylactic gastrostomy was significantly associated with increased late esophageal toxicity. These results are consistent with those of Mekhail et al., who have demonstrated that prophylactic gastrostomy was associated with more dysphagia at 3 and 6 months and significantly increased the need for esophageal dilatation compared with prophylactic nasogastric tube placement. Recently, Rosenthal et al. have recommended considering a nasogastric tube rather than gastrostomy and delaying feeding tube placement as long as possible. Indeed, other authors have suggested that the use of a reactive nasogastric tube is a safe and effective method for managing malnutrition in patients undergoing radiochemotherapy. Considering these results and according to our own findings, we recommend feeding tube placement using a reactive approach based on individual evaluation by the treating radiation oncologist.

With respect to TNM, our univariate analysis showed that patients with stage III–IV cancer lost more weight than did patients with stage I–II cancer. However, this parameter was not significant in the multivariate analysis. Three (4%) patients had tumor recurrence without definitive TNM staging at the time of the analysis, which may have affected our results. We found a clinical trend, but it was not statistically significant. Similar results have been reported by other authors.

It has been published that low PS significantly increased the risk of malnutrition during radiotherapy. In our study, the influence of an ECOG PS score of 2–3 vs. an ECOG PS score of 0–1 on weight loss was analyzed. The ECOG PS score was significantly associated with weight loss at 1 month after treatment. However, it was not a significantly influential factor for weight loss during radiotherapy although there was an evident clinical difference in weight loss during radiotherapy for patients with an ECOG PS score of 2–3 versus patients with an ECOG PS score of 0–1. Indeed, patients with an ECOG PS score of 2–3 lost at least 2 times more weight during radiotherapy than patients with an ECOG PS score of 0–1. This lack of association might be due to the small sample of patients in our study who were classified as having an ECOG PS score of 2–3 (7.8%). In addition, 10 patients had no ECOG PS data available at the time of the analysis. This fact may have affected our results, and these data should therefore be interpreted with caution.

It is noteworthy that minimizing weight loss is important beyond simply improving a patient’s quality of life and providing nutritional support. Moreover, weight loss during radiotherapy is currently an important parameter to be considered during replanning over the course of radiotherapy in patients with head and neck cancer, as it has been shown to have dosimetric advantages.

**Limitations and considerations**

Our results should be interpreted with caution, as the small number of patients in each subgroup make statistical analysis difficult. Moreover, our study included no control arm for comparison because all eligible patients were at high risk of malnutrition during radiotherapy, making it inappropriate for ethical reasons to include a control group. Nevertheless, we can compare our results (albeit indirectly) with those of a previous retrospective cohort analyzed in our department. However, the strengths of the present study include the prospective measurement of weight loss during radiotherapy. In addition, our results indicate that the deterioration of nutritional status (as measured by weight loss) during radiotherapy or 1 month after treatment may be influenced by factors such as the ECOG PS score, the use of chemotherapy, and the cancer location. Thus, we consider that the evaluation of these parameters could be helpful for identifying patients who are at risk of malnutrition during radiotherapy. Despite nutritional counseling and oral nutritional supplementation, the mean patient body weight decreased significantly over time. However, we reported in our previous series a higher mean weight loss (albeit indirect comparison) in patients undergoing radiotherapy without oral nutritional supplementation.

In the present study, radiotherapy was performed postoperatively in 33 (44.6%) patients. Therefore, there was no measurable lesion at the beginning of the treatment in almost 50% of patients. Thus, we could not analyze the relationship between weight loss and response rate. Finally, our findings should be considered hypothesis generating and encourage new prospective clinical research to evaluate and clearly define the role of oral nutritional supplementation and dietetic counseling in patients undergoing radiotherapy.

**Conclusions**

Nutritional assessment is essential prior to radiotherapy. Nutritional status and risk factors such as the head and neck tumor location, the use of chemotherapy, and ECOG PS score should be evaluated because they can influence weight loss during and after radiotherapy, even in patients who do not present with weight loss at the pretreatment evaluation. Despite the use of oral nutritional supplements and dietary counseling, many patients lost weight during treatment. These findings further support the importance of weight control in patients undergoing radiotherapy. Nutritional intervention should be considered in the treatment plan, especially for patients with head and neck tumors. Because patients continue to lose weight 1 month after treatment, their weight after completing radiotherapy should be monitored closely.

Future research evaluating the most effective nutritional intervention to avoid weight loss will help to optimize the management of these patients.
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