Nutritional Status of Patients Undergoing Lung Cancer Operations

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Background. **Patients referred for lung cancer operations were reported to be nutritionally depleted. This may be relevant in determining patient outcome after surgical procedures. A study was undertaken to measure a range of nutritional variables including dietary intake of patients referred to a regional cardiothoracic center for curative lung cancer operations.**

Methods. **Anthropometric measurements, grip strength, fat-free mass (FFM), serum protein concentrations, lymphocyte count, creatinine-height index, subjective global assessment, and data on daily intakes of energy, protein, and vitamin C were collected prospectively. Anthropometric indices were also measured in a group of control patients with mild chronic obstructive pulmonary disease.**

Results. **Sixty patients and 22 control patients were recruited. Weight, skin-fold thickness, and grip strength were not significantly different between patients and control patients, and both groups were similar to the general population. However, 8 patients (13.3%) had a body mass index (BMI) less than 20, and 14 patients (24.1%) had a fat-free mass index less than 15. Serum albumin and transferrin concentrations and lymphocyte count were very rarely depressed but prealbumin and retinol-binding protein levels were below normal in 11.9% and 8.3% of patients, respectively. Thirty percent of patients reported low energy intake, 13% reported a low protein intake, and 61.7% had reduced vitamin C intake.**

Conclusions. **Severe nutritional depletion was uncommon in patients referred for operations for lung cancer and its frequency may have been overestimated in some previous reports. A low intake of vitamin C was common in our patients but its clinical significance is unclear.**

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Lung cancer is often associated with weight loss, and this is of prognostic importance for overall survival [1, 2]. However, only a minority present with operable disease, and studies restricted to these patients have failed to show that preoperative weight loss is of prognostic importance [3]. Nevertheless, other indices of nutritional status may be important in determining surgical outcome in those with operable lung cancer, but to date only a few studies have attempted more detailed nutritional assessment [4–8]. Some of these studies suggest that patients who have undergone lung cancer operations are often nutritionally depleted, and that this may predispose to postoperative, especially pulmonary, complications [4, 5]. Despite these findings nutritional assessment is not a routine part of the preoperative assessment of patients with lung cancer in the United Kingdom.

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We have therefore investigated, in detail, the nutritional status of a group of patients referred for operations for lung cancer. In a companion paper [9] we evaluate the relation of nutritional indices to perioperative mortality and morbidity.

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Material and Methods

Patients

Patients were recruited after referral to the cardiothoracic surgeons at the Freeman Hospital, Newcastle upon Tyne, between January 1995 and May 1997. Because many patients with operable lung cancer also have some degree of chronic obstructive pulmonary disease we also recruited a group of patients with mild chronic obstructive pulmonary disease as control patients for some of the measurements. All patients gave written informed consent, and the local Ethics Committee approved the study. All patients referred for curative resection were eligible but recruitment was limited by geographical factors and the availability of personnel and equipment to complete the preoperative tests.

Protocol

All nutritional measurements apart from dietary records and 24-hour urine collections, were performed on the day of admission for operation. The decision to perform lung resection was made by the surgeon concerned using clinical, radiologic, and spirometric criteria, without reference to the results of the nutritional assessment.

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Nutritional Measurements

Standing height (without shoes), and right elbow width (to assign frame size), were measured using the Holtain anthropometer (Holtain Ltd, Dyfed, UK) [10]. Weight was measured in light clothes without shoes using either electronic scales (Seca 708; Seca, Hamburg, Germany) or an Avery beam balance. Body mass index (BMI) was calculated from weight/height^2. Weight was also expressed as the percent of ideal body weight (%IBW) [11], and compared with weights for a normal population (relative body weight) [10]. Weight change over the 6 months before hospital admission was estimated by patients and expressed as a percentage of previous weight. Skin-fold thickness was measured at four sites (the mean of three attempts at each of triceps, biceps, subscapular, suprailiac) using skin calipers (Holtain Ltd, Dyfed, UK). Midarm circumference was measured using a flexible tape measure, midway between the acromion and olecranon of the right arm. Bone-free midarm muscle area (cm^2) was calculated from the equation: (midarm circumference [cm] $- \pi \times$ triceps skin fold [cm^2]/$4\pi - 10$ if male, or 6.5 if female) [10]. Grip strength was measured using a dynamometer (Model HDA, British Indicators, West Sussex, UK). Subjects performed three maximal grip maneuvers using alternate hands while standing with arms at their side. Patients with deforming or painful conditions of the hands were excluded. The mean of the best attempt from each side was recorded and expressed as a Z score [12].

Fat-free mass (FFM) was estimated by both single frequency bioelectrical impedance analysis (BIA), and four skin-fold thickness measurements using the equations of Durnin and Womersley [13]. BIA was performed at 50 kHz (Bodystat 1500; Bodystat, Douglas, UK) with patients supine with dipole electrodes on the right hand and right foot. BIA and skin-fold methods gave results that were closely correlated ($r = 0.95$) with a linear relation: FFM (skin fold) = 11.9 + 0.79 FFM (BIA). The mean of the two estimates of FFM was used in all but one patient (in whom BIA was not performed). FFM was divided by the height squared to give the fat-free mass index. Measurements of weight, height, skin-fold thickness, midarm circumference and grip strength were made on the control patients as described above, but fat-free mass was estimated using the skin-fold method only.

Serum albumin concentration was measured by the bromocresol green method (Olympus Diagnostic Systems AU5000; Olympus Optical Co (UK) Ltd, South Middlesex, UK) and prealbumin and transferrin were measured using immunonephelometry (Beckman Instruments Array Protein System). The retinol-binding protein was measured using an enzyme-linked immunoadsorbent assay method (RP 1407, Randox Laboratories, Crumlin, UK) and using the normal range of Beetham and colleagues [14]. The lymphocyte count was calculated from the total and the differential white count was obtained by an automatic analyzer.

The 24-hour urine collections were performed at home, and the need for a complete collection was emphasized. To assess completeness, patients were instructed to take three 80 mg tablets of para-amino benzoic acid (PABA) at intervals during the collection period [15]. Wherever possible two 24-hour collections were performed separated by at least 4 days. Urine creatinine concentration was measured using the Jaffé rate method (Beckman Instruments Synchron CX3; Beckman Coulter Inc, Fullerton, CA), and converted into a 24-hour excretion. PABA was assayed by high-performance liquid chromatography [16]. A $\geq 70\%$ recovery of PABA was taken to indicate completeness. The creatinine-height index [17] was calculated from the equations; males: (creatinine excretion [mg/24 hours]/[IBW $\times$ 23]) $\times$ 100, females: (creatinine excretion [mg/24]/[IBW $\times$ 18]) $\times$ 100.

Each patient was assigned a subjective global assessment score based on a structured history and clinical examination, focusing on six nutrition-related features namely, weight loss, dietary intake, gastrointestinal symptoms, nutrition-related functional impairment, and evidence of fat loss or muscle wasting with each graded as either normal, mildly abnormal, or severely abnormal [18]. Patients graded normal in all features were scored A (no depletion), those graded mildly abnormal or severely abnormal in one or more features were scored B (mild to moderate depletion), and if all features were graded mildly abnormal or severely abnormal they were scored C (severe depletion).

Dietary Records

Before hospital admission patients completed a prospective 5-day dietary record (including Saturday and Sunday) using semistructured diet sheets. Emphasis was placed on making a complete record of all that was consumed including the size or, if possible, the weight of portions. The average daily intakes of all major nutrients were calculated using dedicated software ("Microdiet" Mark 9.01, Salford University, Salford, UK). Where no other indication was given, average portion sizes were assumed. Average daily intake of energy, protein, and vitamin C were recorded. Results were compared with reference nutrient intakes (RNI) [19]. Energy intake was expressed as percent of predicted basal metabolic rate (BMR) using Schofield's prediction equations [19]. Protein intake was expressed as percent of RNI based on the ideal body weight (IBW) [11]. The intake of vitamin C (mg) was compared with the RNI of 40 mg per day for nonsmokers, and 100 mg per day for smokers [20].

Statistical Methods

The data were analyzed using the Statview software (version 5.0, SAS Inc, Cary, NC). Means were compared using Student's t test or the Mann-Whitney U test as appropriate. The single group t test was used for comparison with previously published values. The χ^2 test was used to compare proportions. Pearson's linear correlation was used to compare continuous variables. A significance level of p less than 0.05 was adopted.

Table 1. Demographics, Performance Status, and Respiratory Function of 60 Patients With Lung Cancer and 22 Controls With Mild COPD

		Patients	Controls	*p* value
Number		60	22	
Sex	M/F	43/17	12/10	0.14
Age (yrs)	mean (SD)	63.5 (9.1)	53.9 (8.7)	< 0.001
	range	36–80	37–68	
Smoking status	C/E/N[a]	38/20/2	21/1/0	0.02[c]
WHO performance status	0/1/2[b]	14/34/4	n/a	
FEV_1	mean (SD) liters	2.15 (0.7)	2.46 (0.7)	0.06
	mean (SD) % predicted	80.4 (23.1)	78.8 (12.8)	0.76

[a] Current smokers included those who had stopped less than 12 months before recruitment to the study. [b] Number = 52; [c] χ^2 test for trend.

C = current; COPD = chronic obstructive pulmonary disease; E = ex-smoker; F = female; FEV_1 = forced expiratory volume in 1 second; M = male; N = never smoked; n/a = not recorded; SD = standard deviation; WHO = World Health Organization.

Results

Patients

Of 74 patients initially recruited, 4 patients were judged to be too unfit for operations, 1 patient declined an operation, and 1 patient was found on review to have tuberculosis rather than cancer. A further 8 patients were deemed inoperable after further investigations. The remaining 60 patients (Tables 1 and 2) went forward for attempted curative thoracotomy for proved or suspected bronchial carcinoma. This represented about 15% of the total number of patients having attempted curative resection for lung cancer during the recruitment period. Twenty-two control patients with mild chronic obstructive pulmonary disease and no evidence of malignancy or significant comorbidity (Tables 1 and 2) were recruited. All the control patients were ambulatory and only a minority required occasional outpatient supervision.

Demographic and Anthropometric Data

On average the patients with lung cancer were older than the control patients ($p < 0.0001$), and fewer were current smokers ($p = 0.004$). However the two groups had similar proportions of males and females and similar spirometric values. There were no significant differences between the patients and the control patients in any of the anthropometric measurements made (Tables 2 and 3).

Although 8 patients (13.3%) had BMI values less than 20, 9 patients (15%) were obese with BMI more than 30. Four control patients (18.1%) also had BMI less than 20 and 4 control patients had BMI more than 30. Similarly 25.4% of patients were less than 90% IBW, but 47.5% of patients were more than 110% IBW, and 4 of the control patients (18.1%) were less than 90% IBW with 9 control patients (40.9%) more than 110%. The distribution of relative body weight patients and control patients was also similar to that of the general population (Table 3).

Weight loss more than 5% was reported by 14 patients (23.3%), but of these only 3 patients (5%) reported weight loss more than 10%. In contrast 7 patients (11.7%) reported ≥ 5% weight gain over the same period. Similarly 4 control patients (19.0%) reported weight loss more than 5%, and 3 control patients (14.3%) reported ≥ 5% weight gain. There were no significant differences in skin-fold thickness and bone-free midarm muscle area between patients and control patients, and the distribution of these values was similar to that expected in a normal population (Table 3). Mean (standard deviation) FFM in 58 patients was 54.6 (9.2) kg in males and 38.8 (5.6) kg in females. The mean (standard deviation) FFM index for males was 18.6 (2.6), and 15.5 (1.9) for females (Table 2), again similar to values in control patients.

Grip strength was measured in 55 patients. The mean standard deviation strength was 36.7 (8.4) kg in males, and 25.1 (3.4) kg in females. When expressed as a Z score,

Table 2. Weight Change and Other Nutritional Indices

	Patients		Controls		
	No.	Mean (SD)	No.	Mean (SD)	*p* value
BMI (kg/m^2)	60	25.4 (4.7)	22	24.2 (4.2)	0.32
%IBW	59	108.1 (19.5)	22	106.3 (17.2)	0.71
%RBW	59	98.9 (18.1)	22	97.0 (14.9)	0.65
% Weight change	60	−1.4 (6.1)	22	1.0 (5.9)	0.11
FFMI (kg/m^2)	58	17.8 (2.8)	22	17.1 (2.4)	0.30
Grip strength (Z score)	55	0.06 (1.0)	22	−0.04 (1.1)	0.69
Creatinine-height index	19	86.2 (20.5)	n/a	n/a	n/a

BMI = Body mass index (kg/m^2); FFMI = fat-free mass index (kg/m^2); %IBW = % ideal body weight; %RBW = % age-corrected median weight from Frisancho 1984 [10]; SD = standard deviation.

Table 3. Distribution of Weight, Skin-Fold Thickness, and Bone-Free Midarm Muscle Area Compared With Values Obtained From the General Population

	% < Age-Corrected Median[a]			% < Fifth Centile[a]		
	Patients	Controls	*p* value[b]	Patients	Controls	*p* value[b]
Weight	50.8	59.1	0.51	8.5	9.1	0.93
Triceps skin fold	56.9	72.7	0.19	6.9	9.1	0.74
Subscapular skin fold	44.8	59.1	0.25	5.2	4.5	0.91
Bone-free midarm muscle area	44.8	40.9	0.75	3.4	0.0	0.38

[a] Using reference tables of Frisancho 1984 [10]. [b] *p* values are for χ^2-test comparing proportions for patients versus controls.

only one patient's value was more than 2 standard deviations below the expected mean. There was no significant difference in grip strength (absolute or expressed as a Z score) between patients and control patients even when males and females were compared separately (Table 2).

Serum Protein Concentrations and Lymphocyte Count

Values were generally normal, with only 2 patients having subnormal values for albumin, and none for transferrin. A slightly greater proportion had low prealbumin (7 patients, 11.9%) and retinol-binding protein (5 patients, 8.3%). Only one patient had a lymphocyte count below the normal range (Table 4).

Creatinine-Height Index and Subjective Global Assessment

Based on a recovery of PABA of ≥ 70%, only 20 patients' 24-hour urine collections were judged complete. In 19 patients the creatinine-height index was calculated (Table 2) and 13 patients (68%) were less than 100%. The subjective global assessment score showed 30 patients (50%) with some abnormality of nutritional status (score B or C) but only one patient was graded score C (severely depleted) with abnormalities in all features assessed. Of the 29 patients graded score B (mild to moderately depleted), 14 patients reported weight loss of more than 5%, 18 patients had poor subcutaneous fat stores, and 14 patients had evidence of muscle wasting. A smaller number of patients reported reduced dietary intake (8 patients), gastrointestinal symptoms (such as nausea) of more than 2 weeks duration (7 patients), or tiredness and functional impairment (7 patients). Twenty of the 29 patients with score B had abnormalities in two or more features of the subjective global assessment score.

Dietary Records

Forty-seven of 60 patients completed dietary records (Table 5). The distribution of energy intake (Fig 1A) shows that 14 patients (30%) reported daily energy intake less than 120% predicted BMR. Six patients (13%; all male) reported protein intake less than 100% adjusted RNI (Fig 1B). Daily intake of vitamin C was extremely variable with a skewed distribution (Table 5 and Fig 1C). Nineteen patients (40%) reported daily intakes below the RNI of 40 mg per day. Smokers have higher vitamin C requirements and an RNI of 100 mg may be more appropriate [20]. The vitamin C intake of the smokers was similar to that of nonsmokers (median for smokers 40.2 mg versus 57.3 mg for ex-smokers or never smokers, Mann-Whitney *U* test, $p = 0.11$). However, whereas 25 of 31 smokers (81%) consumed less than 100 mg vitamin C only 4 of 16 nonsmokers (25%) consumed less than 40 mg vitamin C ($p = 0.0002$).

Comment

Despite reports of frequent nutritional depletion and subsequent nutrition-related complications after operations among patients with lung cancer, preoperative nutritional assessment is rarely performed. In the present study we report the results of detailed nutritional assessments of 60 patients before attempted curative resection of lung cancer. The patients are similar in age and lung function to those in other series [4, 5] but our results show that nutritional depletion among such patients may be less common than suggested by earlier data.

Criticisms of the Present Study

Inevitably this study was performed on selected patients and the group presented here represents only a minority

Table 4. Serum Protein Concentrations and Lymphocyte Count of Patients With Lung Cancer

	No.	Normal Range	Mean	SD	Number (%) < NR
Albumin	59	38–48 g/L	44.7	3.8	2 (3.4)
Transferrin	59	1.7–3.4 g/L	2.5	0.5	0 (0)
Prealbumin	59	0.18–0.45 g/L	0.28	0.09	7 (11.9)
Retinol-binding protein	59	17–61 mg/L	27.6	8.0	5 (8.5)
Lymphocyte count	59	$1.0–3.0 \times 10^9$/L	2.0	0.8	1 (1.7)

NR = normal range; SD = standard deviation.

Table 5. Preoperative Dietary Intake of Energy, Protein, and Vitamin C in 47 Patients Undergoing Thoracotomy for Lung Cancer

	Mean	Median	Range
Energy intake (MJ/day)	8.5	8.7	3.7–12.6
Energy intake as %BMR[a]	136.5	133.6	55.7–203.0
Protein intake (g/day)	74.1	73.6	35.9–143.8
Protein intake as % adjusted RNI[b]	151.4	153.0	64.4–294.9
Vitamin C intake (mg/day)	80.6	45.8	1.6–502.3

[a]BMR = basal metabolic rate calculated from Schofield equations see [19]; [b] Adjusted RNI = adjusted reference nutrient intake using ideal body weight (see Material and Methods).

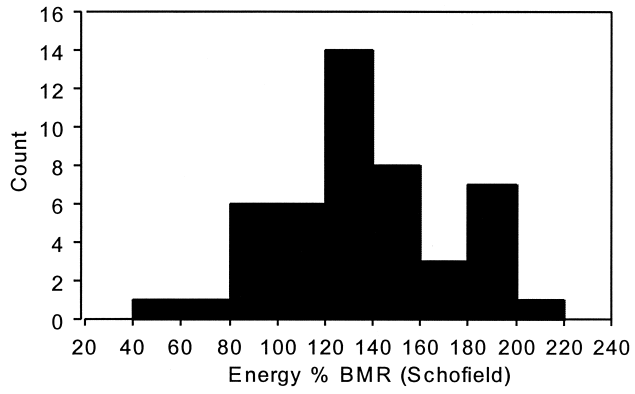
MJ = mega joules.

of those who underwent thoracotomy in our hospital during the period of the study. However, selection was determined entirely by the consent of the patients to be studied and by practical constraints, such as their place of residence and the availability of personnel and equipment, and not by any clinical characteristics of the patients. It should also be emphasized that decisions on operability were made on conventional clinical and investigational criteria, and the results of the additional investigations performed solely for the purpose of the study were not available to the surgeon making the clinical decisions. For this reason we consider that the patients are likely to be representative of those undergoing operations for lung cancer in our institution.

For some of the measurements we also recruited a control group of patients with chronic obstructive pulmonary disease. These were chosen in preference to healthy control patients because many patients undergoing lung cancer operations have coexistent smoking-induced mild to moderate chronic obstructive pulmonary disease and we wished, as far as possible, to control the well-recognized effects of this condition on nutritional status. Although the control patients were on average 10 years older than the main study patients they had a similar degree of generalized airway narrowing, as assessed by forced expiratory volume in 1 second predicted percent. For practical reasons it was not possible to perform the full range of investigations on the control patients group.

Nutritional Measurements

Comparison of patients and control patients showed no significant differences in any of the simple nutritional indices studied. Controlling for the different variables, particularly age, lung function, and smoking habit, is difficult but the similarities between the patients and



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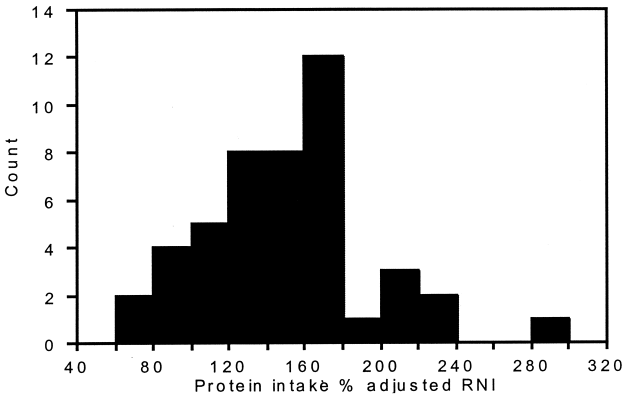

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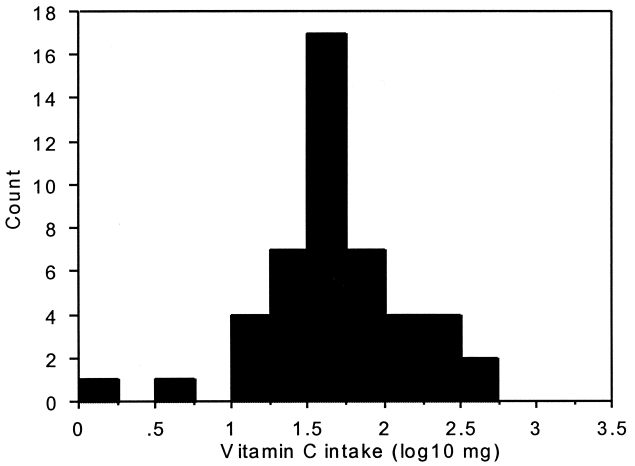

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Fig 1. Dietary intake in 47 patients having thoracotomy for lung cancer. (A) Daily energy intake (as % predicted basal metabolic rate [BMR]). (B) Daily protein intake (as % adjusted reference nutrient intake [RNI]), (see Material and Methods). (C) Daily vitamin C intake (as log_{10} mg).

control patients suggest that early lung cancer does not cause nutritional depletion sufficient to affect anthropometric indices. Furthermore, comparison with population data suggest the anthropometric indices of patients and control patients were similar to expected values.

From our lung cancer patients, 11.6% of men and 17.6% of women had BMI $\leq$ 20. In the general United Kingdom population, 4% of men and 6% of women more than 34 years of age have BMI $\leq$ 20 [21, 22]. However, in those less than 65 years of age, smoking habit and social class are important determinants of BMI [22], and these confounding factors may explain the increased proportion with low BMI.

In the present study, 25.4% of patients had body weights less than 90% IBW, which is often taken to indicate being underweight. However, as the tables for IBW indicate weight associated with maximum longevity and were derived using data from a population of limited age range (25 to 59 years old), their relevance to nutritional status in older groups may be questioned [11]. In contrast, comparison with data from a wider age range of subjects suggests that the weight, skin-fold thickness, and bone-free midarm muscle area of the subjects in the present study are similar to those expected in the general population [10] (Table 2).

Bashir and colleagues [4] reported that of 39 patients having operations for lung cancer, 46% had values of BMI and triceps skin-fold thickness less than the twenty-fifth centile. The reference ranges used for BMI and skin-fold thickness were derived from an earlier large United States community study [23]. Our data analyzed in a similar fashion showed only 35% less than the twenty-fifth centile for BMI, and 36.2% less than the twenty-fifth centile for triceps skin-fold thickness. However, these centile reference ranges are probably inappropriate in older subjects as they were derived from subjects less than 51 years old. Thus the apparent high prevalence of reduced BMI and triceps skin-fold thickness in the study by Bashir and colleagues may be from age-related changes.

A large proportion of patients (23.3%) reported weight loss of more than 5% in the 6 months before admission, yet only 3 patients (5%) reported weight loss more than 10%, values which are broadly similar to those of other series [3, 5]. Very few patients in the present study had depressed serum protein concentrations or lymphocyte count. By contrast, Bashir and colleagues reported 67% with serum transferrin values below the reference range. Their mean of 1.77 g/L is significantly lower than that in the present study (2.53 g/L) ($p < 0.001$) though this may, in part, be from the different assays used [4]. Our serum protein values also contrast with those of Busch and colleagues [5] who found a reduced serum albumin in 15.3% of patients compared to only 3.3% in the present study. Though their patients had similar age and lung function they probably had more advanced disease as extended resection of the chest wall or other major organs was performed in 25 patients (24%) and 28 patients (26%) received perioperative radiotherapy or chemotherapy or both.

The creatinine-height index reflects muscle protein stores and depends on 24-hour urine creatinine excretion. Validation of completeness of the urine collection is difficult and often has been omitted in previous studies. The "PABA check" method developed by Bingham and colleagues to address this problem is widely used [15]. In the present study a PABA recovery greater than 70% was chosen to ensure that at least part of all three 80 mg PABA tablets had been recovered. On this basis only 20 of 33 patients provided a satisfactory 24-hour urine collection emphasizing the importance of validating completeness of collection. Bashir and colleagues [4] did not assess completeness of urine collections and therefore may have underestimated creatinine excretion. The validated results of the creatinine-height index in the present study showed that only 7 of 19 patients (36.9%) were less than 80%, compared with 23 of 39 patients (59%) of those in the study by Bashir and colleagues ($p = 0.11$).

Overall our results suggest that only a minority of patients undergoing operations for lung cancer have nutritional abnormalities, with rates generally lower than previously reported. Part of the explanation for the differences between this and earlier studies may be improvements in staging and thus selection of patients, which in turn may be reflected by improved nutritional status. As marked weight loss or other evidence of severe nutritional depletion is unusual in those referred for curative operations for lung cancer, its presence should stimulate a more thorough review of the staging investigations.

Dietary Records

The values for energy intake in the present study were similar to, or greater than, those reported for the United Kingdom population [21, 22]. Energy requirements vary with exercise and illness but even minimal activity would lead to a total energy requirement of at least 120% BMR, and habitual energy intake below this level is unlikely to meet requirements. Furthermore some studies have shown that estimates of BMR derived from normal patients may underestimate actual values for those with operable lung cancer [8]. Thus those reporting energy intakes of less than 120% BMR (the low-energy reporters group) would be expected to lose weight through catabolism if their records are accurate. In the present study 14 patients (30%) fell into the low energy reporters (LER) group including 50% of men and 27% of women, and of these, 9 patients reported weight loss. The mean weight loss of the LER group was 2.8% compared with 0.5% in the remainder, but this did not reach statistical significance. Further validation of energy intake and direct measurement of energy expenditure would be required to establish the true energy balance among these patients, but the possibility remains that a minority may have markedly inadequate energy intake.

When protein intake was expressed as percent adjusted RNI, only 6 patients (13%) reported intakes less than 100%. We found no correlation between protein intake (as g/day, g/kg/day or as percent-adjusted RNI)

and serum concentration of either prealbumin or retinol-binding protein despite reports that such short-lived serum proteins may be responsive to dietary intake [24].

Vitamin C is known to be important for wound healing and records of intake were included for this reason. The results of the present study suggest that a large proportion of those having operations for lung cancer have inadequate vitamin C intake, and that this may be a particular problem for smokers as they metabolize vitamin C more quickly [25].

In summary, diet records suggest that a minority of our patients had negative energy balance and potentially inadequate protein intake or both, whereas many had low vitamin C intake. If nutritional depletion is important in determining complications after operations, identifying the relevant individuals and improving the patient's oral intake in the period before the operation might be beneficial.

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