Nutritional support during the hospital stay reduces mortality in patients with different types of cancers: Secondary analysis of a prospective randomized trial

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- 48
- 49 **Running title:** Nutritional support in cancer patients

50 Abstract

51 Introduction: Nutritional support in patients with cancer aims at improving quality of 52 life. Whether use of nutritional support is also effective in improving clinical outcomes 53 remains understudied.

54 **Methods:** In this preplanned secondary analysis of patients with cancer included in a 55 prospective, randomized-controlled, Swiss, multicenter trial (EFFORT), we compared 56 protocol-guided individualized nutritional support (intervention group) to standard 57 hospital food (control group) regarding mortality at 30-day (primary endpoint) and 58 other clinical outcomes.

59 **Results:** We analyzed 506 patients with a main admission diagnosis of cancer,

60 including lung cancer (n=113), gastrointestinal tumors (n=84), hematological

61 malignancies (n=108) and other types of cancer (n=201). Nutritional risk based on

62 Nutritional Risk Screening [NRS 2002] was an independent predictor for mortality

63 over 180 days with a (age-, sex-, center-, type of cancer-, tumor activity- and

treatment-) adjusted hazard ratio of 1.29 (95% CI 1.09 to 1.54; p=0.004) per point

65 increase in NRS. In the 30-day follow-up period, 50 patients (19.9%) died in the

66 control group compared to 36 (14.1%) in the intervention group resulting in an

adjusted odds ratio of 0.57 (95% CI 0.35 to 0.94; p=0.027). Interaction tests did not

show significant differences in mortality across the cancer type subgroups. Nutritional

69 support also significantly improved functional outcomes and quality of life measures.

70 **Conclusion:** Compared to usual hospital nutrition without nutrition support,

individualized nutritional support reduced the risk for mortality and improved

functional and quality of life outcomes in cancer patients with increased nutritional

risk. These data further support the inclusion of nutritional care in cancer

74 management guidelines.

75 **Keywords**: nutrition, outcomes, cancer, malnutrition, randomized trial,

76 **Highlights**

77 78 Nutritional risk in patients with cancer was an independent prognostic indicator •

79 regarding 6-month mortality

- 80 In patients with cancer and increased nutritional risk, individualized nutritional •
- support during the hospital stay reduced mortality 81
- 82 Nutritional support also improved functional and quality of life outcomes. •
- 83
- 84

alt

85 Introduction

Effective anti-cancer strategies are based on combination of disease-modifying therapies and supportive and palliative care. The goal of supportive and palliative care is to address needs of patients with cancer and thus enhance quality of life.[1] Early and simultaneous delivery of disease-modifying therapy and palliative care has been demonstrated to improve clinical outcomes. However, the specific role of nutritional care in favoring a better outcome in patients with cancer remains understudied.

93 Malnutrition affects about 30% of oncological and hematological malignancy patients 94 and is associated with higher mortality, impaired functional status and longer hospital 95 stays.[2-4] The clinical presentation of malnutrition in patients with cancer may vary 96 from loss of appetite and/or weight, to loss of muscle mass with sarcopenia, to 97 severe tumor cachexia. [5] Several factors put patients with cancer at high 98 malnutrition risk including tumor-derived cytokine release causing loss of appetite 99 and anorexia, and side effects of cancer treatment again interfering with appetite and 100 normal food intake.[6-8] In addition, once admitted to the hospital, patients with 101 cancer are at high risk for further deterioration of the nutritional status due to fasting 102 for diagnostic studies, treatment side effects and overall suboptimal nutritional 103 management.

To prevent adverse clinical outcomes associated with malnutrition, the European Society for Clinical Nutrition and Metabolism (ESPEN) recommends identifying cancer patients at nutritional risk through early screening, followed by nutritional counseling and nutritional support.[6, 7] Different screening tools are recommended for this purpose, including the Nutritional Risk Screening (NRS 2002).[9] [10, 11] However, there is relatively little evidence regarding this recommendation for the population of hospitalized patients with cancer and previous trial data has been

111	somewhat inconclusive.[5, 12] While some trials looking at patients with colorectal
112	cancer found improved outcomes associated with nutritional support
113	interventions,[13, 14] other trials have not provided evidence that in favor of using
114	nutritional interventions.[12] Whether malnutrition is indeed a modifiable risk factor
115	and improved by nutritional interventions has therefore been questioned.
116	Herein, we performed a preplanned secondary analysis of a randomised multicentre
117	trial in Switzerland [4, 15], investigating the effect of nutritional support during the
118	hospital stay compared to usual care hospital food on mortality and other clinical
119	outcomes in patients with different types of cancer.
120	
121	Methods
122	Study design
123	This is a secondary analysis of the subset of patients with cancer as a main
124	admission diagnosis included in the EFFORT (Effect of early nutritional support on
125	Frailty, Functional Outcomes and Recovery of malnourished medical inpatients)
126	trial.[4] Effort was an investigator-initiated, open-label, randomized, controlled trial in
127	eight Swiss hospitals investigating the effect of early individual nutritional support on
128	medical outcomes in patients at risk of malnutrition. The trial protocol and the results
129	of the main trial, as well as secondary outcomes, have been published previously.[4,
130	11, 16-22] The Ethics Committee of Northwest and Central Switzerland (EKNZ)
131	approved the study protocol in January 2014 (EKNZ; 2014_001).
132	
133	Patient population
134	All participating centers had an active malnutrition screening in place using the NRS
135	2002. This score is a well-established tool for assessing malnutrition risk based on a
136	patient's nutritional status and disease severity with a total score ranging from 0-7

137 points.[9, 11] A score of 3 points or more indicates increased nutritional risk. For the 138 purpose of this study, we stratified the nutritional risk of patients based on NRS (i.e., 139 moderate, high and very high risk defined as NRS 3, 4 and \geq 5 points). 140 For the initial trial, we enrolled adult patients with a NRS total score ≥3 points and an 141 expected length of hospital stay of >4 days. Exclusion criteria were initial admission 142 to intensive care units or surgical units; patients with terminal illness; admission diagnosis of anorexia nervosa, acute pancreatitis, acute liver failure, cystic fibrosis or 143 144 stem-cell transplantation and history of gastric bypass surgery. Also, patients unable 145 to ingest food orally, already receiving nutritional support or existing contraindications 146 for nutritional support, and those previously included in the study were excluded. All 147 patients eligible for this secondary analysis had a documented main admission 148 diagnosis of cancer, which was confirmed and validated by a complete chart review 149 after hospital discharge. The reporting of the proportion of patients with cancer thus 150 differs from the original trial where diagnosis was based on admission data only. We 151 also classified patients based on the type of cancer based on a complete review of 152 the medical records. Tumor activity was defined as "active" if patients received 153 antitumor treatment in the previous year or if the first diagnosis of cancer was made 154 on admission. We also included "non-active" patients with cancer in the analysis if 155 above mentioned definition was not met, but cancer was a main admission diagnosis. 156

157 **Procedures**

After trial inclusion, we randomized patients by use of an interactive web system 1:1 to the intervention group receiving individualised nutritional support according to an implementation protocol[23], or the control group receiving usual hospital food without nutritional support. In the intervention group, nutritional support was initiated as soon as possible after randomization within 48 hours of hospital admission.

163 Patients received individualized nutritional support to reach protein and energy goals, 164 defined for each patient upon hospital admission by a trained registered dietician. 165 Energy requirements were predicted using the weight-adjusted Harris-Benedict 166 equation.[24] Daily protein intake was set at 1.2–1.5 g/kg body weight to adjust for 167 higher protein breakdown during acute disease[25], with lower targets for patients 168 with acute renal failure (0.8 g per kg of body weight). To reach these goals, an 169 individual nutritional plan was developed by a trained registered dietician for each 170 patient. This plan was initially based on oral nutrition provided by the hospital kitchen 171 (including food adjustment according to patient preferences, food fortification (e.g., 172 enrichment of hospital food by adding protein powder) and providing patients with 173 between-meal snacks) and oral nutritional supplements[26, 27]. A further increase in 174 nutritional support to enteral tube feeding or parenteral feeding was recommended if 175 at least 75% of energy and protein targets could not be reached through oral feeding 176 within 5 days. Nutritional intake was reassessed every 24-48 h throughout the 177 hospital stay by a trained registered dietician based on daily food records for each 178 patient. Upon hospital discharge, patients received dietary counselling and, if 179 indicated, a prescription for oral nutritional supplements in the outpatient setting. 180 There was no planned follow-up regarding nutritional intake in the outpatient setting. 181 Control group patients received standard hospital food according to their ability and 182 desire to eat, with no nutritional consultation and no recommendation for additional 183 nutritional support.

184

185 Outcomes

The primary endpoint was all-cause mortality within 30 days. The main secondary
endpoints was adverse outcome, a composite endpoint predefined for the initial
trial[4, 16], that includes all-cause mortality, admission to the intensive care unit from

189 the medical ward, non-elective hospital readmission after discharge, and major 190 complications including adjudicated nosocomial infection, respiratory failure, a major 191 cardiovascular event (e.g., stroke, intracranial bleeding, cardiac arrest, myocardial 192 infarction) or pulmonary embolism, acute renal failure, gastro-intestinal events 193 (including hemorrhage, intestinal perforation, acute pancreatitis) or a decline in 194 functional status of 10% or more from admission to day 30 measured by the Barthel's 195 index. A detailed description of outcomes is provided in the **Appendix**. 196 Additional hospital outcomes included admission to intensive care, non-elective 197 hospital readmission within 30 days and mean length of hospital stay and functional 198 outcome such as a decline in functional status of 10% or more within 30 days, and 199 functional impairment (measured by the Barthel's Index and quality of life assessed 200 with the European Quality of Life 5 Dimensions Index, including the EQ-5D VAS 201 visual-analogue scale). Barthel's scores range from 0 to 100, with higher scores 202 indicating better performance of activities of daily living. The European Quality of Life 203 5 Dimensions index (EQ-5D) ranges from 0 to 100, with higher scores indicating 204 better quality of life. EQ-5D VAS (including visual-analogue scale) ranges from 0 to 205 100, with higher scores indicating better health status.

As an additional secondary outcome, we also assessed mortality after a follow-up time of 6 month, where we had information from 1995 of 2028 patients (98%)

included in the initial trial.[17]

209

210 Statistical analyses

For this secondary analysis, we used a similar statistical approach as in the original trial[4, 16]. We tested the hypothesis that individualised nutritional support is superior to usual hospital food with regard to mortality and other secondary endpoints. We performed all analyses in the intention-to-treat population, which included all patients

215 with a main admission diagnosis of cancer who had undergone randomisation unless 216 they withdrew consent. Categorical variables are presented as counts (percentages) 217 and continuous variables as means and standard deviations (SD). 218 First, we investigated the prognostic implications of nutritional risk by calculation of 219 regression analysis regarding NRS and clinical outcomes adjusted for important 220 confounders (patient age, sex, study center, cancer subgroups, tumor activity and 221 treatment). We calculated Cox regression models for time-to-event analyses with 222 reporting of hazard ratios (HR) and illustrated the probability of all-cause mortality in 223 Kaplan-Meier survival curves. We used logistic regression for binary data and linear 224 regression for continuous outcomes. Second, we compared outcomes between 225 randomization arms by means of regression analysis adjusted for study center, 226 Barthel's Index at admission and NRS at baseline (as predefined in our protocol).[15] 227 We used logistic regression for all binary outcomes with reporting of odds ratios 228 (ORs) and corresponding 95% confidence intervals (Cl's), and linear regression for 229 continuous outcomes with reporting of coefficients (differences). Finally, we 230 conducted subgroup analyses for patient age, sex, risk for malnutrition by NRS, 231 cancer type subgroups, tumor activity and treatment, and reason for admission. We 232 calculated interaction analysis to test for effect modification by main prognostic 233 factors. 234 All statistical analyses were performed using STATA 15.1 (Stata Corp, College 235 Station, TX, USA). A P value < 0.05 (for a 2-sided test) was considered to indicate

237

236

238 **Results**

statistical significance.

This analysis includes 506 patients with a confirmed main diagnosis of cancer at
hospital admission. with a confirmed main diagnosis of cancer at hospital admission

241 (255 intervention group patients and 251 controls) from an original cohort of 2028 242 EFFORT trial patients **Supplemental Figure 1** shows the detailed patient flow. 243 Overall, patients had different types of cancers and a high burden of comorbidities. 244 The most frequent types of cancer were lung cancer (n=113), hematological 245 malignancies (n=108) and gastrointestinal tumors (n=84). The most common reason 246 for hospitalization was cancer treatment, new cancer diagnosis and failure to thrive 247 associated with the cancer diagnosis. Detailed baseline characteristics are shown in 248
 Table 1 for both groups.
 249 Caloric and protein intake of patients during the in-hospital study period is listed in 250 Appendix, Supplemental Table 1. Compared to control group patients, intervention 251 group patients had a significantly higher mean caloric (1411 vs 1154 kcal/day) and 252 protein (52.7 vs 44.2 g protein/day) intake during the index hospital stay. 253 254 Association of nutritional risk with mortality and other endpoints 255 Nutritional risk as measured using NRS 2002 was strongly associated with mortality 256 over the 180-day follow-up with an adjusted HR of 1.37 (95% CI 1.15 to 1.61), 257 p<0.001) per point increase in NRS. Figure 1 shows the time to death stratified by 258 NRS with shorter time until death with higher NRS groups. We also observed an 259 association between NRS and the composite endpoint of adverse outcomes 260 (adjusted OR per point increase in NRS of 1.42 [95% CI 1.11 to 1.83]; p=0.006). 261 Similar results were found for mean length of hospital stay, functional decline and 262 impairment in quality of life (Table 2). 263 264 Effect of nutritional support on clinical outcomes

A total of 50 patients (19.9%) in the control group died within 30 days compared to 36 (14.1%) in the intervention group resulting in an adjusted OR of 0.57 [95% CI 0.35 to

267 0.94; p=0.027] (Table 3). These results were also illustrated in Kaplan Meier

268 estimates stratified by randomization group (**Figure 2**).

- 269 We also investigated effects of nutritional support regarding mortality over 6 months
- of follow-up. We recorded 128 (52.7%) deaths in the control group compared to 115
- death (47.3%) in the intervention group resulting in an adjusted HR of 0.83 (95%CI
- 272 0.65 to 1.08, p=0.18) (see **supplemental figure 3** in the Appendix).
- 273 Compared to the intervention group, there was a higher risk in the control group for
- functional decline in activities of daily living (defined by Barthel scale) (adjusted OR
- 275 0.59 [95% CI 0.38 to 0.93]; p=0.021). In addition, patients receiving nutritional
- support showed significant improvements in quality of life as defined by EQ-5D Index
- 277 (adjusted coefficient 0.08 [95% CI 0.01 to 0.15]; p=0.016) and by EQ-5D VAS
- 278 (adjusted coefficient 6.16 [95% CI 0.51 to 11.8]; p=0.033). No significant differences
- were found for other secondary outcomes including the composite outcome, length of
- hospital stay and non-elective hospital readmission (**Table 3**).
- 281

282 Subgroup analysis for mortality and adverse outcome

We also performed several pre-planned subgroup analyses to investigate whether
effects of nutritional support were similar among patients with different

- 285 sociodemographic characteristics, different types of cancers, tumor activity and
- treatment, and reason for admission. Overall, there was no evidence for effect
- modification among subgroups for mortality (**Figure 3**). Similarly, regarding the
- 288 composite endpoint of adverse outcome, no significant effect in interaction analysis
- was found for any subgroup (**Appendix, Supplemental Figure 2**).
- 290
- 291

292 **Discussion**

293 The principal findings of this secondary analysis of a large-scale, randomized, 294 controlled nutritional trial focusing on hospitalized patients with different types of 295 cancer are twofold. First, nutritional risk was strongly associated with mortality at 6 296 months, which was independent of different other prognostic indicators and cancer 297 activity. Second, compared to a control group of patients receiving standard hospital 298 food without nutritional support, the use of individualized nutritional support to reach 299 nutritional goals resulted in a significant improvement in mortality and other functional 300 outcomes at short-term. These effects were consistent among different types of 301 cancers and other predefined subgroups.

302

303 Several aspects of this analysis are noteworthy. Firstly, we observed a strong 304 increase in mortality in patients with higher nutritional risk, corroborating previous 305 reports in this patient population. [10, 11, 28] Indeed, patients with an NRS of ≥5 306 points had a 19% higher risk of long-term mortality compared to those with 3 points. 307 The results remained similar when adjusting the analysis for other prognostic 308 indicators and cancer-associated factors, suggesting that nutritional status 309 independently predict outcome in this population of patients. Further strong 310 associations were found between NRS and other clinically-relevant secondary 311 outcomes. Risk screening by NRS thus allows to identify a group of cancer patients 312 at highest risk for adverse outcome where clinical attention is indicated.

313

Second, While the negative prognostic implications of deteriorating nutritional status
in patients with cancer have previously been demonstrated, conclusive evidence
regarding clinical effects of nutritional support in this population is currently scarce
with international societies giving only weak recommendations regarding

318 treatment.[6, 7, 28] Importantly, clinicians may be reluctant to provide nutritional 319 support to patients with cancer with low appetite but rather focus on anti-cancer 320 treatments to improve the underlying problem.[12] Herein, our data provide evidence 321 that patients show strong benefit from nutritional support, with a greater than 5% 322 reduction in mortality (i.e., from 19.9% to 14.1%). Interestingly, this effect was found 323 independent of type of cancer and cancer activity, although some of the subgroups 324 investigated were small and do not allow firm conclusions. Clearly, the subgroup 325 analysis was underpowered with risks for type II error. In fact, visual inspection of the 326 forest plots suggests some numerical heterogeneities (e.g., patients with only 327 moderate nutritional risk [NRS 3 points] and patients with cancer-associated pain as 328 their main reasons for admission) pointing to possible lack of effect or even harm 329 regarding adverse outcome in these subgroups. Importantly, there may be 330 differences among cancer patients regarding the potential benefit from nutrition. For 331 example, patients with chronic catabolism driven by cancer-related systemic 332 inflammation may be less likely to show benefit from nutritional support. Yet, we did 333 not collect such data in our trial for more specific phenotyping of patients and were 334 thus not able to test this hypothesis. Clearly, prospective trials are needed with more 335 homogenous groups of patients regarding type of cancer and treatment to 336 understand which clinical situation provides the best opportunity for intervention. 337 Nevertheless, our results support the clinical relevance of simultaneously addressing 338 patients' oncological and nutritional needs, and provide a possible explanation to the 339 recently reported discrepancies in outcomes for patients enrolled in clinical trials and 340 those in registries.[29] Considering that patients with cancer with comorbidities, 341 including malnutrition, are less likely to be offered to participate to a clinical trial,[30] 342 prevention and treatment of malnutrition may confer additional benefits. Also,

343 concurrent care may enhance patients with cancer' quality of life, an issue frequently
344 overlooked even under the protected umbrella of a clinical trial.[31]

345

346 Third, unlike other trials investigating the effect of specific nutritional formulas, [32] we 347 used a variety of nutritional support strategies with the support of trained dieticians to 348 reach nutritional goals. Our trial does thus not provide evidence for effects of single 349 nutritional components, but rather suggests that the overall strategy of providing 350 nutritional support to reach different nutritional goals during a hospital stay for an 351 acute illness is beneficial for patients with cancer. Because nutritional support after 352 discharge was not standardized, and not part of the main protocol focusing on in-353 hospital nutrition, the impact of continuing nutrition in the outpatient setting remains 354 undefined from our data. Clearly, there is need for additional trials validating our 355 findings in the population of cancer patients including also continued outpatient 356 treatment.

357

Fourth, we also found significant improvements in functional and quality of life outcomes – a majority concern of patients with cancer [33-37]. A previous trial found no effect of nutritional intervention on quality of life and physical function in patients with cancer[38] and meta-analysis on the topic reported heterogenous results with insufficient overall evidence[39]. Again, as these previous studies focused on different populations and clinical settings, it is important to continue nutritional research in this highly vulnerable population of patients.

365

Fifth, similar to our study, previous reports found a high prevalence of malnutrition in
different types of cancer including gastrointestinal cancers (e.g., pancreatic and
gastroesophageal cancer), and in lung cancer and hematological malignancies.[40] A

majority of studies focused on patients with gastrointestinal malignancies as
malnutrition may appear early in these types of cancers[41] and nutrition may also
improve surgical outcomes for this population[42]. As a limitation, we excluded
surgical patients in our initial trial.

373

374 Another important population is patients receiving antitumor treatment because 375 treatment-related severe side-effects may lead to anorexia and weight loss.[43-46] 376 Several studies with patients undergoing specific therapies have reported improved 377 outcomes with nutritional support[14, 47]. One Danish trial described the association 378 between intensive, individual dietary counseling and improved weight maintenance 379 and higher provision of protein and energy amounts in patients with gynecologic, 380 gastric or esophageal cancer being treated with radiotherapy and/or 381 chemotherapy.[48, 49] These findings are in line with our report as we also had a 382 large proportion of patients receiving antitumor therapy in the previous year. 383 384 Our trial has several strengths and limitations. The main strength is that it is a 385 secondary analysis of a prospective, randomized trial consisting of a large 386 unselected and heterogeneous population. As a result, our patient sample represents 387 a broad spectrum of cancer sites, treatment types and disease severities. 388 Study limitations include the lack of blinding of participants and personnel, and some 389 variation in the achievement of the individualized caloric and protein. We also 390 excluded patients at end-of-life due to ethical considerations. Regarding tumor 391 activity, we did not break down the individual antitumor therapies. Also, our control 392 group did not receive nutritional care, including supplements, which is standard in 393 some hospitals for patients at nutritional risk. Thus, it is not clear whether our 394 intervention would have been superior to such a standard. While mortality effects

395 were significant in our analysis, we did not find strong reductions in the risk for 396 adverse outcome – a composite endpoint including severe complications, ICU 397 admission, functional decline and rehospitalization in addition to mortality. In our 398 main trial, we decided to focus on in-hospital nutrition only and nutritional support 399 after discharge was not standardized, and not part of the main protocol. The impact 400 of continuing nutrition in the outpatient setting thus remains undefined from our data. 401 Clearly, there is need for additional trials validating our findings in the population of 402 cancer patients including also continued outpatient treatment. Finally, as only 403 inpatients from the medical ward were included, we have no information about 404 patients primarily hospitalized for surgery. 405 406 In conclusion, among hospitalized patients with cancer at nutritional risk, 407 individualized nutritional support reduced the risk for mortality as compared to 408 standard hospital food. These data support malnutrition screening upon hospital 409 admission followed by an individualized nutritional support strategy in this vulnerable 410 patient population. Also, they strengthen the evidence in favor of inclusion of 411 nutritional care in the multi-professional and multidisciplinary management of patients

412 with cancer and in relevant guidelines.

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421

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429

430 Author contributions

LB, CB, JH and PS were responsible for the data analysis and interpretation of this secondary analysis. LB, CB, JH and PS drafted the final manuscript with all authors contributing to critical revision of the manuscript. PS was responsible for obtaining funding. AB, LH, MB, NK, PT were involved in data collection and approved the final version of the manuscript.

FG, CH, VP, SB, SS, MB, CH, RT, JR, DA, NR, JD were involved in drafting the trial
protocol, supervision of study sites, drafting of the final manuscript and approving the
final version of the manuscript of the original EFFORT trial.

ZS and BM were involved in obtaining funding, drafting the trial protocol, supervision
of study sites, drafting of the final manuscript of the original EFFORT trial and
approved the final version of the current manuscript. The corresponding authors had
full access to all the data used and had a shared final responsibility for the accuracy
of the analysed data.

- 444
- The data underlying this article cannot be shared publicly due to the privacy of
- 446 patients who participated in this trial. The data will be shared on reasonable request
- to the corresponding author.
- 448

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590 Tables and Figure Legend

- 591
- 592 Figure 1. Kaplan-Meier estimates stratified by NRS 2002 for 180-day mortality
- 593 **Figure 2.** Kaplan-Meier estimates of cumulative incidence of all-cause mortality
- 594 within 30 days according to randomization group
- 595 **Figure 3.** Odds ratios for mortality within 30 days in prespecified subgroups
- 596

597 **Table 1: Patient baseline characteristics**BMI = Body Mass Index, NRS = 598 Nutritional Risk Screening 2002; *Other hematological malignomas include essential

599 Thrombozytopenia, Multiple Myeloma and similar illnesses; **Others include

600 pleuramesothelioma, Cancer of unknown Primary and similar

601602 Table 2: Association of NRS score and primary and secondary outcomes.

Data represent # of events (%), unless otherwise stated. All odds ratios were

604 calculated with a logistic regression for binary data and linear regression for

605 continuous data. Models were adjusted for patient age, sex, study center, cancer 606 subgroups, tumor activity and treatment. Continuous values as median and IQR.

607 categorical/binary values as absolute number and percentage.

⁶⁰⁸ *Combined adverse outcome was a composite endpoint and includes all-cause

609 mortality, admission to the intensive care unit from the medical ward, non-elective

610 hospital readmission after discharge, and major complications including adjudicated

- nosocomial infection, respiratory failure, a major cardiovascular event (i.e., stroke,
- 612 intracranial bleeding, cardiac arrest, myocardial infarction) or pulmonary embolism,
- 613 acute renal failure, gastro-intestinal events (including hemorrhage, intestinal
- 614 perforation, acute pancreatitis) or a decline in functional status of 10% or more from
- admission to day 30 measured by the Barthel's index

616 NRS= Nutritional Risk Screening, EQ-5D= Euroquol-5 Dimensions, VAS= Visual
 617 Analogue Scale

618

619 Table 3: Effect of nutritional support on primary and secondary outcomes

Data are number of events (%), unless otherwise stated. All odds ratios were

- 621 calculated with a logistic regression for binary data and linear regression for
- 622 continuous data. Models were adjusted for initial nutritional risk screening score and
- 623 study center. Continuous values as median and IQR, categorical/binary values as
- 624 absolute number and percentage.
- ⁶²⁵ *Combined adverse outcome was a composite endpoint and includes all-cause
- 626 mortality, admission to the intensive care unit from the medical ward, non-elective
- 627 hospital readmission after discharge, and major complications including adjudicated
- 628 nosocomial infection, respiratory failure, a major cardiovascular event (i.e., stroke,
- 629 intracranial bleeding, cardiac arrest, myocardial infarction) or pulmonary embolism,
- acute renal failure, gastro-intestinal events (including hemorrhage, intestinal
- 631 perforation, acute pancreatitis) or a decline in functional status of 10% or more from 632 admission to day 30 measured by the Barthel's index
- 633 NRS= Nutritional Risk Screening 2002, EQ-5D= Euroquol-5 Dimensions, VAS=
- 634 Visual Analogue Scale

Table 1: Patient baseline characteristics

	Control group	Intervention group
N	251	255
Sociodemographics		
Male sex (%)	152 (60.6%)	146 (57.3%)
Mean age (years) (SD)	71.5 (12.4)	69.2 (13.5)
Nutritional assessment		
Mean BMI (kg/m2) (SD)	24.8 (4.4)	24.2 (5.0)
Mean bodyweight (kg) (SD)	72.8 (13.3)	69.7 (15.8)
NRS 2002 score (%)		
3 points	56 (22.3%)	69 (27.1%)
4 points	88 (35.1%)	88 (34.5%)
5 points	87 (34.7%)	81 (31.8%)
>5 points	20 (8.0%)	17 (6.7%)
Tumor subgroups		
Lung cancer	49 (19.5%)	64 (25.1%)
Gastrointestinal tumors	51 (20.3%)	33 (12.9%)
Colon carcinoma	15 (6.0%)	10 (3.9%)
Rectum carcinoma	14 (5.6%)	6 (2.4%)
Pancreas carcinoma	13 (5.2%)	6 (2.4%)
Hepatocellular carcinoma	9 (3.6%)	11 (4.3%)
Hematological tumors	54 (21.5%)	54 (21.2%)
Leukemia	13 (5.2%)	18 (7.1%)
Lymphoma	39 (15.5%)	34 (13.3%)
Other hematological malignomas*	2 (0.8%)	2 (0.8%)
Other tumors	97 (38.6%)	104 (40.8%)
Breast carcinoma	19 (7.6%)	17 (6.7%)
Prostate carcinoma	16 (6.4%)	20 (7.8%)
Gynecological cancers	12 (4.8%)	14 (5.5%)
Kidney and urothelial cancers	14 (5.6%)	12 (4.7%)
Ear, nose, throat Carcinoma	4 (1.6%)	6 (2.4%)
Genital cancer	4 (1.6%)	3 (1.2%)
Skin cancer	5 (2.0%)	1 (0.4%)
Others**	23 (9.2%)	31 (12.2%)
Tumor activity and treatment		
Inactive	35 (13.9%)	23 (9.0%)
Active	216 (86.1%)	232 (91.0%)
Reason for admission		
Cancer associated failure to thrive	58 (23.1%)	62 (24.3%)
Cancer associated pain	36 (14.3%)	30 (11.8%)
Cancer associated fever and infection	36 (14.3%)	31 (12.2%)
Cancer treatment and other indications	66 (26.3%)	80 (31.4%)
First diagnosis for cancer	55 (21.9%)	52 (20.4%)

BMI = Body Mass Index, NRS = Nutritional Risk Screening 2002; *Other hematological malignomas include essential Thrombozytopenia, Multiple Myeloma and similar illnesses; **Others include pleuramesothelioma, Cancer of unknown Primary and similar

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Table 2: Association of NRS score and primary and secondary outcomes.

	NRS 3 points (N=125)	NRS 4 points (N=176)	NRS >4 points (N=205)	type of analysis	Regression analysis per point increase in NRS (unadjusted) (95% Cl und p-value)	Regression analysis per point increase in NRS (adjusted) (95% CI and p-value)
Primary outcome						
All-cause mortality within 30 days	15 (12.0%)	31 (17.6%)	40 (19.5%)	HR	1.27 (0.96 to 1.67), p=0.093	1.20 (0.91 to 1.60), p=0.199
Secondary outcomes						
All-cause mortality within 180 days	47 (37.6%)	80 (45.5%)	116 (56.6%)	HR	1.33 (1.17 to 1.56), p=0.001	1.37 (1.15 to 1.61), p=0.0001
*Combined adverse outcome within 30 days	32 (25.6%)	64 (36.4%)	83 (40.5%)	OR	1.38 (1.09 to 1.74), p=0.008	1.42 (1.11 to 1.83), p=0.006
Additional hospital outcome				0		
Admission to an intensive care unit within 30 days	3 (2.4%)	6 (3.4%)	1 (0.5%)	OR	0.56 (0.25 to 1.25), p=0.159	0.53 (0.21 to 1.34), p=0.180
Non-elective hospital readmission within 30 days	11 (8.8%)	16 (9.1%)	26 (12.7%)	HR	1.23 (0.87 to 1.75), p=0.245	1.29 (0.90 to 1.86), p=0.162
Mean length of index hospital stay (days)	9.0 (6.8)	10.7 (7.4)	11.0 (7.5)	coefficient	0.91 (0.11 to 1.72), p=0.027	1.04 (0.22 to 1.87), p=0.013
Functional outcome						
Decline in functional status of $\ge 10\%$ from admission to day 30	17 (13.6%)	40 (22.7%)	55 (26.8%)	OR	1.47 (1.11 to 1.94), p=0.006	1.50 (1.12 to 2.01), p=0.006
Mean Barthel score at day 30 (points)	96.12 (8.89)	95.06 (10.39)	93.90 (11.28)	Coefficient	-1.11 (-2.26 to 0.04), p=0.058	-1.53 (-2.69 to -0.36), p=0.010
Mean EQ-5D Index at day 30 (points)	0.72 (0.35)	0.65 (0.39)	0.60 (0.39)	Coefficient	-0.06 (0.1 to -0.02), p=0.008	-0.06 (-0.10 to -0.02), p=0.009
Mean EQ-5D VAS at day 30 (points)	51 (28)	45 (30)	42 (31)	Coefficient	-4.74 (-8.36 to -1.13), p=0.01	-4.18 (-7.88 to -0.47), p=0.027

Data represent # of events (%), unless otherwise stated. All odds ratios were calculated with a logistic regression for binary data and linear regression for continuous data. Models were adjusted for patient age, sex, study center, cancer subgroups, tumor activity and treatment. Continuous values as median and IQR, categorical/binary values as absolute number and percentage.

*Combined adverse outcome was a composite endpoint and includes all-cause mortality, admission to the intensive care unit from the medical ward, non-elective hospital readmission after discharge, and major complications including adjudicated nosocomial infection, respiratory failure, a major cardiovascular event (i.e., stroke, intracranial bleeding, cardiac arrest, myocardial infarction) or pulmonary embolism, acute renal failure, gastro-intestinal events (including hemorrhage, intestinal perforation, acute pancreatitis) or a decline in functional status of 10% or more from admission to day 30 measured by the Barthel's index NRS= Nutritional Risk Screening, EQ-5D= Euroquol-5 Dimensions, VAS= Visual Analogue Scale

Table 3: Effect of nutritional support on primary and secondary outcomes

	Control (N=251)	Intervention group (N=255)	type of analysis	Regression analysis (adjusted) (95% CI and p-value)
Primary outcome				
All-cause mortality within 30 days	50 (19.9%)	36 (14.1%)	OR	0.57 (0.35 to 0.94), p=0.027
Secondary outcomes			<u>ç</u>	
Clinical outcome			0	
Combined adverse outcome within 30 days	93 (37.1%)	86 (33.7%)	OR	0.81 (0.56 to 1.19), p=0.288
Additional hospital outcomes				
Admission to an intensive care unit within 30 days	6 (2.4%)	4 (1.6%)	OR	0.62 (0.16 to 2.5), p=0.503
Non-elective hospital readmission within 30 days	22 (8.8%)	31 (12.2%)	OR	1.53 (0.85 to 2.75), p=0.159
Mean length of stay stay of index hospital stay (days)	10.4 (6.9)	10.4 (7.8)	HR	1.14 (0.93 to 1.40), p=0.206
Functional outcome				
Decline in functional status of \geq 10% from admission to day 30	67 (26.7%)	45 (17.6%)	OR	0.59 (0.38 to 0.93), p=0.021
Mean Barthel Index score at day 30 (points)	94.72 (10.68)	94.98 (10.21)	Coefficient	0.6 (-1.16 to 2.36), p=0.506
Mean EQ-5D Index at day 30 (points)	0.62 (0.39)	0.67 (0.37)	Coefficient	0.08 (0.01 to 0.15), p=0.016
Mean EQ-5D VAS at day 30 (points)	43 (30)	48 (29)	Coefficient	6.16 (0.51 to 11.8), p=0.033
Long-term mortality				
All-cause mortality within 180 days	128 (52.7%)	115 (47.3%)	HR	0.83 (0.65 to 1.08), p=0.18

Data are number of events (%), unless otherwise stated. All odds ratios were calculated with a logistic regression for binary data and linear regression for continuous data. Models were adjusted for initial nutritional risk screening score and study center. Continuous values as median and IQR, categorical/binary values as absolute number and percentage.

*Combined adverse outcome was a composite endpoint and includes all-cause mortality, admission to the intensive care unit from the medical ward, non-elective hospital readmission after discharge, and major complications including adjudicated nosocomial infection, respiratory failure, a major cardiovascular event (i.e., stroke, intracranial bleeding, cardiac arrest, myocardial infarction) or pulmonary embolism, acute renal failure, gastro-intestinal events (including hemorrhage, intestinal perforation, acute pancreatitis) or a decline in functional status of 10% or more from admission to day 30 measured by the Barthel's index NRS= Nutritional Risk Screening 2002, EQ-5D= Euroquol-5 Dimensions, VAS= Visual Analogue Scale



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	Control group (n/N (%))	Intervention group (n/N (%))		Adjusted odds ratic (95% Cl)	P interaction
All patients	50/251 (19.9%)	36/255 (14.1%)	+	0.57 (0.35 to 0.94)	
Age (years)					
Age <65	8/58 (14%)	10/87 (11%)	_ _	0.66 (0.20 to 2.17)	0.902
Age 65-75	15/78 (19%)	10/68 (15%)	→	0.53 (0.20 to 1.40)	
Age>75	27/115 (23.5%)	16/100 (16.0%)	.	0.59 (0.28 to 1.23)	
Sex					
Male	34/152 (22.4%)	23/146 (15.8%)		0.51 (0.27 to 0.98)	0.714
Female	16/99 (16.2%)	13/109 (11.9%)	→	0.49 (0.20 to 1.22)	
Risk for malnutrition					
NRS 3 points	6/56 (11%)	9/69 (13%)	+	1.33 (0.42 to 4.19)	0.891
NRS 4 points	22/88 (25%)	9/88 (10%)	←	0.19 (0.07 to 0.52)	
NRS ≥5 points	22/107 (20.6%)	18/98 (18.4%)	_ .	0.83 (0.38 to 1.82)	
Cancer subgroups					
Lung cancer	10/49 (20%)	13/64 (20%)		0.98 (0.28 to 3.35)	0.532
Gastrointestinal cancers	12/51 (24%)	4/33 (12%)	→	0.25 (0.06 to 1.10)	0.459
Hematological cancers	11/54 (20%)	6/54 (11%)	→	0.38 (0.11 to 1.38)	0.334
Other cancers	17/97 (17.5%)	13/104 (12.5%)		0.65 (0.27 to 1.55)	0.409
Tumoractivity and treatment					
Inactive	4/35 (11%)	1/23 (4%)	• — — — — — — — — — — — — — — — — — — —	0.25 (0.02 to 2.95)	0.273
Active	46/216 (21.3%)	35/232 (15.1%)	_	0.56 (0.33 to 0.94)	
Reason for admission					
Cancer associated failure to thrive	19/58 (33%)	12/62 (19%)	—	0.36 (0.13 to 0.95)	0.427
Cancer associated pain	9/36 (25%)	5/30 (17%)	+	0.85 (0.17 to 4.27)	0.794
Cancer associated fever and infection	3/36 (8%)	4/31 (13%)	-	0.41 (0.03 to 6.12)	0.190
Cancer treatment and other reasons	8/66 (12%)	8/80 (10%)	_ +	0.74 (0.21 to 2.63)	0.470
First diagnosis for cancer	11/55 (20%)	7/52 (13%)	+ .	0.55 (0.16 to 1.81)	0.731

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reduces mortality

Nutrition support increases mortality

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