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Malnutrition and Obesity in Pediatric Oncology Patients: Causes, Consequences, and Interventions

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Abstract

In children with cancer, suboptimal nutrition states are common consequences of the disease and its treatment. These nutrition states have been attributed to a number of etiologies dependent on the patient's tumor type and treatment, and are associated with increased morbidity and mortality. Interventions vary from psychosocial to pharmacological and surgical management. Further research is necessary to understand the epidemiology and etiology of these nutrition states. Of great importance is the development and implementation of effective interventions to optimize nutritional status among children with cancer during and after therapy.

Keywords

nutrition; pediatric oncology; obesity; malnutrition; support care

MALNUTRITION AND CHEMOTHERAPY

Definition and Detection

Although malnutrition is a common complication of pediatric cancer and its treatment, firm criteria defining this state are not universally used. The Children's Oncology Group (COG) Nutrition Committee has established categories of nutritional status and an algorithm for nutritional intervention based on body mass index (BMI), weight for length or height (WT/LT), or percentile ideal body weight for height or length (%IBW) [1]. In comparison to BMI, arm anthropometric measurement has been shown to be a more sensitive indicator of malnutrition among children with cancer, especially in those with tumor burden [2,3]. Despite the recommendation that triceps skinfolds be incorporated into the assessment of pediatric patients with cancer [4], a COG survey of nutritional practices found that only 5% (6/125) of institutions measured triceps skinfolds. Incorporation of arm anthropometric measurement in nutrition algorithms is urged. Femoral quadriceps muscle ultrasonography [5], bioelectrical impedance [6], total body potassium counting [7], and dual energy x-ray

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CONFLICTS OF INTEREST STATEMENT
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absorptiometry scanning [8] have all been used to analyze body composition, but larger studies in groups of children with cancer are lacking.

Laboratory indices such as serum albumin and prealbumin are common components of nutritional assessment [9], despite reports of their clinical limitations [10] and lack of correlation with other indices of nutritional status [11]. Still, arguments have been made for the utility of prealbumin measurements in patients with acute lymphoblastic leukemia (ALL) [12] or solid tumors [13]. In a prospective study of children in Latin America, the use of albumin adjunct to anthropometric measurements increased the sensitivity of malnutrition criteria [3]. Overall, the role of serial biochemical measurements in the continuing assessment of nutritional status in children with cancer remains unclear, and further studies in this area are warranted.

Subtle changes in micronutrients and metabolism may occur even in the absence of deviations from normal in height and weight. Low plasma 1,25-dihydroxy vitamin D levels have been demonstrated in children with ALL at diagnosis, consistent with the effect of leukemia on vitamin D metabolism and bone turnover [14]. Low levels of antioxidant nutrients, including vitamins A, C, E, as well as zinc and selenium, have also been observed in ALL patients at diagnosis and during treatment [15]. Additional study pertaining to the prevalence and consequences of micronutrient deficiencies in children with cancer is needed.

Prevalence and Risk Factors

It remains difficult to derive a clear understanding of the prevalence of malnutrition because most studies have focused on children with leukemia where generally small sample sizes have been used, and various methods have been employed to assess nutritional status. In a review of 11 observational studies, Brinkshma et al. [16] found that leukemia patients had the lowest prevalence of malnutrition, about 5%–10% at diagnosis and 0%–5% during treatment. Children with neuroblastoma demonstrated the highest rate at diagnosis, at 50%, whereas for children with other solid tumors, the estimated prevalence was 0%–30%. The etiologies of weight loss and malnutrition at diagnosis are variable; possible causes are energy deficiency and/or inflammation leading to loss of fat and fat free mass [16]. Table I lists factors associated with malnutrition risk in children with cancer based on tumor type, treatment modality, and patient demographics.

Etiologies of Malnutrition

F actors leading to energy deficiency in children with cancer include insufficient intake, increased metabolic rate, altered physical activity, and inflammation [16]. Several studies have demonstrated lower energy intake at diagnosis among patients compared with healthy controls, but similar energy intake during patient treatment [17–20]. Only one study, however, tested the relationship between altered energy intake and nutritional state [20], and further study in this area is warranted. Depression-related anorexia is another likely, but thus far unstudied, cause of low energy intake.

Among nine reviewed studies of metabolic rate in pediatric cancer patients, an increased metabolic rate could not be demonstrated in childhood cancer patients during treatment [16]. Conclusions about metabolic rate at diagnosis are conflicting, with reports of both normal [17,19] and elevated rates [21]. Also, no studies have tested the relationship between metabolic rate and changes in BMI.

Table II lists factors contributing to cancer cachexia, a phenomenon linked to inflammation resulting in decline in muscle mass and functional status, in pediatric oncology patients. Tumor and host released cytokines such as tumor necrosis factor α (TNF-α), interleukin-1

(IL-1), interleukin-6 (IL-6), and interferon-γ (IFN-γ) are often used in the assessment of inflammation. The few available studies of inflammation in children with cancer have demonstrated increased TNF-α [59], IL-1 receptors [83], and protein turnover [103], though no relationship with fat or muscle mass [59] or nutritional status [83, 103] was found. Overall, only separate elements of energy balance have been studied, and few studies have tested the relationship between energy deficiency and nutritional status.

Consequences of Malnutrition During Treatment

Many studies, but not all [22,23], have found that malnutrition is a negative prognostic factor and reduces survival in direct proportion to its extent [24–26]. Malnutrition and underweight have been associated with inferior survival in children with metastatic diseases [25,27], ALL [28–30], and acute myeloid leukemia [AML] [31]. In a recent large prospective study of children with newly diagnosed cancer in Central America (n = 1787), children were stratified into three nutritional categories on the basis of arm anthropometric measurements and/or serum albumin levels. Event-free survival rates at 2 years differed significantly between adequately nourished and severely depleted children (65% vs. 48%) [$P < 0.001$] [3]. Malnutrition in children with cancer has also been associated with decreased treatment tolerance [27,32], unfavorable response to chemotherapy [4,32–34], treatment delays [27], increased risk of infection [35–37], and diminished quality of life [25,38]. Large prospective studies on the effect of nutritional status on morbidity and mortality among children are lacking.

Strategies for Intervention

The goals of nutritional intervention in children are to promote normal development, maintain body stores as close to ideal as possible, and maximize functional status as a child receives treatment. At present, there are no agreed-upon parameters regarding the criteria for, timing of, and duration of nutritional interventions in pediatric oncology patients [39]. Table III lists the indications, advantages, and disadvantages of oral, enteral tube, and parenteral interventions for children with cancer.

Behavioral and Educational Interventions—In clinical trials among adults with cancer, individualized nutritional intervention by a registered dietitian significantly improved nutritional status [40], weight maintenance, and quality of life [41]. Clinical studies are needed of how registered dietitian's interventions in children with cancer affect nutritional status and clinical outcome. Unfortunately, institutions nationwide cited lack of a registered dietitian as the biggest barrier to providing optimal nutritional support [9].

Behavioral modification techniques have been used successfully among children with cystic fibrosis, for whom early and aggressive nutritional therapy is a cornerstone of treatment. In one study, a 9-week intervention that used self-monitoring and goal setting resulted in a significant increase in average energy intake and weight gain [42]. Although malnutrition in children with cystic fibrosis arises from distinct etiologies, such interventions could be adapted for pediatric oncology patients.

Education of the healthcare team is important, and a review of nutrition support methods in pediatric oncology is available in print for physicians and other healthcare providers [4]. For nurses, "Nutrition in Children and Young People with Cancer" (Royal College of Nursing 2010) is available online [43]. Useful resources for caregivers include "Nutrition for the Child with Cancer" (American Cancer Society, 2010) and "Helping Your Child to Eat" (Royal Marsden Hospital, 2004), both available online.

Oral Pharmacologic Interventions—Oral appetite-enhancing agents have been studied in small groups of pediatric cancer patients. In one study of children with cancer cachexia (n = 66), daily administration of the agents cyproheptadine hydrochloride and/or megestrol acetate resulted in significant weight gain at 4 weeks with response rates greater than 75% [44]. A randomized controlled trial of megestrol acetate in malnourished children with cancer is underway (ClinicalTrials.gov Identifier [CTID] NCT00439101), as is a randomized controlled trial evaluating cyproheptadine hydrochloride in children newly diagnosed with cancer (CTID: NCT01132547).

The benefits of these appetite-enhancing agents have not been universally demonstrated in oncology populations, however. In one trial, adults with advanced cancer (n = 295) treated with cyproheptadine hydrochloride showed reduced nausea but no weight gain [45]. In adult [46] and pediatric populations [47,48], studies involving megestrol acetate treatment have documented adrenal suppression, glucose intolerance, edema, thromboembolism, and the absence of gain in lean body mass. The prevalence of and risk factors for these adverse effects remain unknown and are barriers to the wider use of these measures.

Omega-3 fatty acid supplementation with eicosapentaenoic acid to promote weight gain has been studied in a small number of children with cancer (n = 52), with significant resultant weight gain [49]. A randomized controlled trial investigating the effects of enteral administration of omega-3 fatty acid supplementation on nutritional status in children with ALL is under way (CTID: NCT01051154).

In a prospective study that included children with ALL, suboptimal total antioxidant status during treatment was associated with significantly increased toxicity from chemotherapy and decreased quality of life [15]. Greater antioxidant intake in the same cohort resulted in fewer therapy delays, less toxicity, and lower incidence of infection [50]. Studies of antioxidant levels among children with other types of malignancies and larger prospective studies on the effect of increased antioxidant intake on clinical outcome are needed.

Enteral Tube and Parenteral Interventions—Recommendations have been made to consider proactive enteral tube feeding (EN) among children with cancer at high risk of malnourishment [1,32]. In retrospective studies, early EN intervention has been associated with less nutritional decline in children with medulloblastoma [32] or osteosarcoma [51]. Among the latter, children with percutaneous endoscopic gastrostomy (PEG) placed at diagnosis and EN lasting throughout chemotherapy [n = 29] also tended to have fewer surgical complications, relapses, and deaths. Further prospective studies are warranted to assess the effect of proactive EN on nutritional status and clinical outcome.

PEG feeding is a well-tolerated method of EN in children with cancer [52]. In a retrospective study of pediatric oncology patients who received PEG (n = 74), 75% experienced weight gain or stabilization, with complication rates similar to those of a control neurological group (62% versus 76%, respectively) [51]. Elsewhere, the frequency of infection with PEG was reported as comparable to that of parenteral nutrition [53]. Larger prospective studies are needed to confirm these results.

Compared to parenteral nutrition, some clinical trials have found EN to be safer and more cost-effective, even in the setting of bone marrow transplantation [54–56]. On the other hand, a Cochrane review of eight controlled trials of nutritional support in 159 children with cancer concluded there was limited evidence to suggest parenteral nutrition is more effective than enteral nutrition in well nourished children [57]. Larger clinical trials with well-defined outcome measures comparing enteral and parenteral methods of nutritional support in children undergoing chemotherapy are greatly needed.

OBESITY AND CHEMOTHERAPY

Obesity at Diagnosis

Definition, Prevalence, and Population at Risk—According to the American Academy of Pediatrics, children may be considered obese on the basis of a BMI standard deviation score (BMI-SDS) of greater than the 95th percentile [58]. Other definitions of obesity include WT/LT greater than the 90th percentile or %IBW greater than 120% [1]. Large retrospective studies have demonstrated a prevalence of obesity at diagnosis ranging from 8.6% of children with ALL [59] to 14.8% of children with AML [31]. Comparably less is known about the prevalence of obesity among children with solid and brain tumors. In adults, obesity is a risk factor for certain types of malignancies [60]; the effect of obesity on risk of childhood cancer has not been rigorously examined.

In children, obesity at diagnosis of cancer is associated with increased risk of obesity at treatment end and in survivorship [61]. All efforts should be taken to prevent obesity in survivorship because obese adults experience impaired glucose tolerance, diabetes mellitus, hypertension, cardiovascular disease, higher rates of some forms of cancer, and inferior survival when they develop cancer [60]. This is in addition to the finding that adult survivors of childhood cancer experience higher risks of cardiovascular disease and second malignancies than do their siblings [62,63]. The burden of obesity in childhood cancer survivors is not entirely known, and a request has been made for longitudinal prospective studies on body composition in patients from diagnosis through follow-up [64].

Consequences of Chemotherapy in Children Who Are Obese at Diagnosis—Obesity at diagnosis has been associated with inferior survival rates in children with cancer. In a retrospective analysis of 768 children with AML, Lange et al. [31] found that obese children had significantly inferior survival rates compared with middle-weight patients (BMI-SDS = 11th–94th percentiles) The authors attributed this to higher rates of treatment-related mortality in the obese group, although there was no evidence that these children had received excess chemotherapy. In a subsequent retrospective study of 4,260 children with ALL, Butturini et al. [59] found that overweight patients with a diagnosis of cancer after age 10 had a significantly lower mean 5-year event-free survival rate and a higher mean risk of relapse than did normal weight patients. Overweight was not associated with dose alterations, treatment delays, or increased toxicity, and the authors hypothesized that the higher risk of relapse might be due to differing pharmacokinetics of the drugs used in ALL maintenance. In contrast, Hijiya et al. [22] found in a retrospective study of 621 children treated for ALL that BMI had no influence on outcome or on the pharmacokinetics of several chemotherapeutic agents. Studies of chemotherapy pharmacokinetics with clinical correlations in obese children with cancer are limited to glucocorticoids, etoposide [22,65], methotrexate, teniposide, and doxorubicin [22]. Retrospective reviews of finished studies are needed to assess survival and toxicities associated with obesity and to determine the optimal methods of calculating chemotherapy dosages among obese children.

Mechanisms underlying the association between obesity and cancer are only starting to be understood. Obesity-related lymphokines can increase treatment toxicity by altering inflammation and can influence tumor biology by promoting angiogenesis and cell growth [66]. Glucose itself regulates the cell cycle [67], and high fasting levels of insulin have been associated with increased recurrences in adults with ALL [68]. Among obese children with ALL, a trend for higher initial white blood cell counts compared with normal-weight peers has been demonstrated and is consistent with an effect of obesity on cell growth [59].

Treatment-Related Obesity

Definition, Prevalence, and Population at Risk—Children with ALL or brain tumors have been the subjects of most studies of obesity risk during and after treatment because of the high risk of hypothalamic-pituitary axis damage secondary to cancer therapies or to primary tumor location. In one retrospective study of children treated for ALL (n = 102), the proportion of overweight patients increased steadily from 15% at diagnosis to 40% by treatment end [69]. Similarly, in a study of 46 children who underwent successful treatment for suprasellar brain tumors, the prevalence of overweight increased more than seven-fold from 6% at diagnosis to 43% at follow-up [70]. Table I lists factors associated with high risk of adiposity. Longitudinal studies of changes in body composition during treatment are needed to identify risk factors and optimal timing for interventions.

Etiologies of Treatment-Related Obesity—In children with ALL, excessive weight gain has been attributed to growth hormone [GH] deficiency/hypothalamic-pituitary axis damage due to cranial RT [71], leptin deregulation [72], exposure to corticosteroids [73], reduced physical activity [74,75], and poor dietary habits during survivorship [76]. Female survivors of ALL or brain tumors, especially if treated with cranial RT, demonstrate increased prevalence of obesity compared with the general population [64,77]. Cranial RT has been strongly associated with GH deficiency, which leads to raised leptin and fasting insulin concentrations, altered body fat distribution (abdominal obesity), and dyslipidemia (particularly in women) [78].

Excessive weight gain during ALL treatment is often attributed to the adverse effects of glucocorticoids [GC], which are known to promote adiposity in central fat and directly blunt adipocyte insulin sensitivity [79]. In small cross-sectional studies, childhood ALL-survivors demonstrated increased fat mass during the first years after corticosteroid treatment [64], but it is not clear whether this change was temporary or persistent. ALL patients have also had higher levels of energy intake and less physical activity during treatment with GC than they did on nontreatment days and compared with healthy controls [80]. The influences of glucocorticoids on body composition are still uncertain, and longitudinal prospective research to elucidate the long-term effect of corticosteroids on body habitus is warranted.

Children treated for ALL, compared with controls and with children treated for other malignancies, demonstrate significantly reduced total daily energy expenditure [81,82]. There has been no strong evidence of abnormalities in basal metabolic rate in long-term survivors of childhood ALL [82], and in general, researchers have concluded that decreased levels of physical activity account for the alterations in total daily energy expenditure. The mechanisms responsible for the patterns of reduced activity remain unknown; exercise intolerance, lower self-esteem, and habitual inactivity have all been postulated [81]. The effect of physical activity intervention on outcome has yet to be assessed.

Brain tumor survivors with hypothalamic insult present with an often intractable form of weight gain termed “hypothalamic obesity.” The cause of weight gain is not completely understood but is thought to arise from damage to the ventromedial hypothalamus, the center responsible for interpreting afferent vagal and hormonal signals from the liver, gut, pancreas, and adipose tissue. This leads to dysregulation of pancreatic beta-cell vagally mediated insulin release and insulin hypersecretion with enhanced weight gain. Significantly reduced physical activity has been observed in craniopharyngioma patients [83] and has been associated with overall reduction in sympathetic tone [84].

Strategies for Intervention

Studies have called for clinical guidelines to prevent and manage obesity in children with cancer, especially ALL or brain tumors [70,85]. Figure 1 illustrates the major causes and consequences of obesity in pediatric cancer patients and/or survivors with recommended interventions.

In one study, children with brain tumors and high risk of hypothalamic obesity (n = 39) attended a comprehensive care clinic that provided family-centered treatment with assessment by a dietician, behavior psychologist, neuropsychologist, exercise consultant, and an endocrinologist. During the time that children attended this clinic, their median % weight gain, % IBW, and rate of increase in % BMI were significantly lower than were the values obtained during standard care [86]. There is great need for similar models to be applied to diverse pediatric oncology populations.

Novel interventions involving interactive electronic media are being implemented increasingly as a youth-friendly means of promoting behavioral change [87]. A video game intervention has successfully increased medication adherence in children with cancer [88], and in another instance, an ongoing clinical trial is investigating the ways in which weight-related tailored text messages as part of a weight management program affect BMI among obese adolescents [CTID: NCT01448551].

Interventions directed towards hypothalamic obesity are challenging, since no standard pharmacological or surgical intervention has consistently had positive outcomes [89]. Lustig et al. [90] used octreotide, which prevents insulin hypersecretion, in a randomized controlled study in children with hypothalamic obesity after successful treatment for brain tumors and showed significant reductions in weight gain. However, this was followed by a larger multinational study that demonstrated no efficacy in the primary end-point of change in BMI [89]. Recently, a pilot trial of daily diazoxide and metformin among 9 pediatric patients with craniopharyngioma and hypothalamic obesity found significantly less weight gain in the treatment group (+1.2 ± 5.9 kg versus +9.5 ± 2.7 kg; P = .004) [91]. Surgery is usually considered the last resort, and varying efficacy with malabsorptive procedures such as gastric bypass [92] has been reported. In general, randomized controlled trials of, and experience with, interventions are rare, and treatment algorithms remain to be clarified.

CONCLUSION

Nutritional intervention for children with cancer is challenging and is compounded by an incomplete understanding of the etiologies of suboptimal nutritional states in this population and a paucity of evidence regarding the clinical efficacy of interventions. Despite a number of publicized guidelines suggesting effective approaches to nutritional support [93–96], pediatric care centers nationwide vary widely with respect to nutritional practice and management, which are frequently based on opinion instead of evidence [9]. Ladas et al. [97] described the establishment of The International Committee on Nutrition & Health for Children with Cancer, a multinational group of allied health professionals that will strive to develop modifiable nutritional guidelines and education tools, will facilitate research collaboration, and will establish administrative support. These efforts are direly needed.

Further investigation of the epidemiology and etiologies of malnutrition and obesity, in conjunction with the initiation of well-designed clinical trials to investigate efficacy of nutritional interventions, will enable the development and validation of uniform nutrition protocols. These are necessary to optimize nutritional status in children with cancer during and after treatment and to leverage this modifiable factor to improve quality of life and survival for pediatric cancer patients and survivors.

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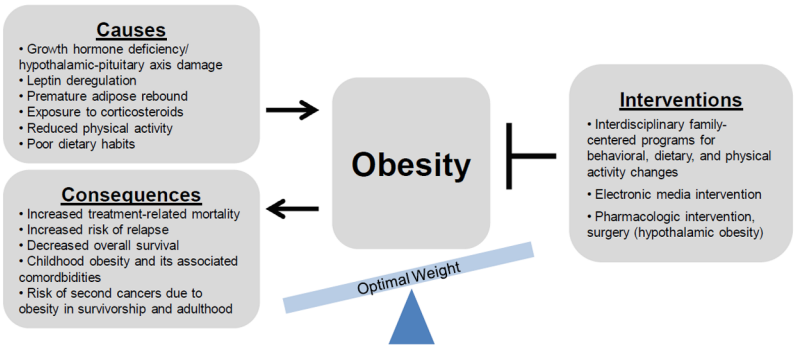

Fig. 1. Major causes and consequences of obesity in childhood cancer patients and/or survivors with recommended interventions

Obesity is attributed to multiple etiologies depending on patient tumor type and treatment. Due to metabolic and neuroendocrine alterations, increased energy intake, and decreased energy expenditure, fat mass increases. Obesity is associated with increased morbidity and mortality in patients and survivors. Behavioral, pharmacologic, and/or surgical interventions are necessary to prevent, reduce, and diminish excessive weight gain during and following treatment.

Table I

Factors Associated with High Nutritional Risk in Children with Cancer Undergoing Chemotherapy

	High risk of malnutrition	**High risk of adiposity**
Tumor type	Presentation with and/or undergoing treatment for: • Solid tumors in advanced stages – Neuroblastoma – Wilms tumor – Rhabdomyosarcoma • Advanced-stage Ewing sarcoma • Multiple relapsed and some high-risk leukemias • Head and neck tumors • Diencephalic tumors • Post–stem cell transplantation (graft vs. host disease)	Presentation with and/or undergoing treatment for: • Central nervous system tumors – Craniopharyngioma – Medulloblastoma – Astrocytoma Undergoing treatment for: • Acute lymphoblastic leukemia • Ependymoma • Nasopharynx carcinoma • Sarcoma • Lymphoma • Disseminated testicular cancer
Treatment modality	• Irradiation to the gastrointestinal tract • Major abdominal surgery • Bone marrow transplantation • Intense frequent intervals (≤3 weeks) of chemotherapy in the absence of corticosteroids	• Extensive brain surgery • High-dose cranial/craniospinal radiotherapy • Total body or abdominal radiotherapy • Prolonged corticosteroid therapy with large doses, or other drugs that increase body fat stores
Patient demographics	• Infancy • Low socioeconomic status • Lack of family or health support system	• Brain tumors[70,79] – Female – Greater than average BMI at diagnosis • ALL[59] – Age less than 10 yr at diagnosis – Hispanic – Male

Table II

Factors Contributing to Cancer Cachexia in Pediatric Oncology Patients

Sources of energy imbalance	Potential mechanisms
Inflammation causing low energy intake and/or anorexia	• Cytokines released by tumor, immune, and stromal cells alter central nervous system transmitters and affect appetite – Tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1) may increase levels of corticotrophin-releasing peptide, a neurotransmitter that suppresses food intake[98] • Modulation of gastric motility and emptying – Direct effect on gastrointestinal system – Alteration of efferent signals regulating satiety; IL-1 blocks feeding stimulated by neuropeptide Y[99]
Metabolic and endocrine alterations leading to increased catabolic drive	• Carbohydrate metabolism – Increased fasting insulin levels – Increased glucose demand • Protein metabolism – Loss of normal compensatory protein conservation mechanisms seen in starvation – Increased whole-body protein catabolism – Increased protein catabolism in muscle cells – Decreased regulators of muscle protein synthesis • Fat metabolism – Accelerated lipolysis driven by inflammatory cytokine inhibition of lipoprotein lipase; TNF-α and Il-6 implicated[4] – Increased rate of fat oxidation and clearance – Decreased lipoprotein-lipase, may shift energy burden to lean body mass • Disease burden – Metabolic demands of tumor in progressive disease

Table III

Indications, Advantages, and Disadvantages of Oral, Nasogastric, Gastrostomy, and Parenteral Nutritional Interventions for Children with Cancer

	Indications	Advantages	Disadvantages
Oral feeding	• Meeting >90%–100% of estimated energy needs • Stable or improving nutritional status	• Physiologic • Noninvasive	
Nasogastric (NG) tube feeding	• Weight loss or inability to meet >90% of energy requirements for 3–5 d • Severe mucositis for <3 d • Normal gastric emptying	• Easy tube insertion • Larger reservoir capacity in stomach	• Risk of pulmonary aspiration • Cosmetically unappealing • Discomfort in nose/pharynx • Displacement with emesis • Risk of vancomycin-resistant enterococcus (VRE) colonization[100]
Gastrostomy or jejunostomy feeding	• Weight loss or inability to meet >90% of energy needs through NG tube for 3–5 d • Severe mucositis and/or emesis anticipated • Undergoing head/neck radiotherapy • Swallowing dysfunction • Prolonged dependence on enteral feeding • Unwilling to accept NG tube • Older patients who would prefer this route	In comparison with parenteral nutrition[54] • Better maintenance of structural and functional integrity of intestinal tract • Lower risk of bacterial translocation • Greater ease and safety of administration • More physiologic and efficient use of nutrient substrates • Lower risk of hepatobiliary complications • Increased cost-effectiveness	• Local irritation • Peristomal infection • Gastric leakage • Tube migration • Potential fistula after tube removal • Surgery needed for surgical gastrostomies • Risk of VRE colonization[100]
Parenteral nutrition	• Compromised gastrointestinal absorption and/or unable to tolerate enteral feeds for >3–5 d • Severe vomiting and diarrhea • Severe pancreatitis • Graft vs. host disease affecting the intestinal tract • Paralytic ileus	• Bypasses compromised gastrointestinal tract • Does not require direct accessibility to gastrointestinal tract	• Risk of septic complications • Mechanical complications of catheter placement • Hemodynamic abnormalities • Metabolic and electrolyte abnormalities • Hepatobiliary complications • Metabolic bone disease