INDICATIONS AND CONTRAINDICATIONS

F. Bozzetti (IT)
Parenteral nutrition in oncology patients
indications and contraindications

Federico Bozzetti

ESPEN 2016
HISTORICAL BACKGROUND

1971

2001
AGA Medical Position Statement: PN (Gastroenterology 2012;121;966)
AGA Technical Review on PN (Gastroenterology 2012;121;970)

2016
The new ESPEN GLs on Clinical Nutrition in Oncology (Arends et al)
### Table 5. Meta-Analysis of Oncologic Trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Absolute risk difference</th>
<th>Confidence intervals</th>
<th>Number of studies (patients) included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0%</td>
<td>-5%, +5%</td>
<td>19 (1050)</td>
</tr>
<tr>
<td>Total complication rate</td>
<td>+40%</td>
<td>+14%, +66%</td>
<td>8 (333)</td>
</tr>
<tr>
<td>Infectious complication rate</td>
<td>+18%</td>
<td>+8%, +23%</td>
<td>18 (823)</td>
</tr>
<tr>
<td>Tumor response</td>
<td>-7%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-12%, -1%</td>
<td>15&lt;sup&gt;d&lt;/sup&gt; (910)</td>
</tr>
<tr>
<td>Bone marrow toxicity</td>
<td>+22%</td>
<td>-10%, +54%</td>
<td>3 (134)</td>
</tr>
<tr>
<td>Gastrointestinal toxicity</td>
<td>+1%</td>
<td>-9%, +11%</td>
<td>6 (310)</td>
</tr>
</tbody>
</table>

<sup>a</sup>This represents the difference between the outcome in the treated group and the control group; a negative number represents a benefit for the treated group.

<sup>b</sup>Although 1 bone marrow transplantation trial reported an improved survival, this was not demonstrated when all 4 trials were combined; absolute risk difference equaled -5% (-14%, +5%). Only 3 of these trials provided parenteral nutrition during the time when the transplantation was performed; when only these 3 trials were combined, absolute risk difference equaled -9% (-22%, +4%).

<sup>c</sup>A negative absolute risk difference indicates that the response rate in the control group was higher than in the recipients of the parenteral nutrition.

<sup>d</sup>13 of these 15 RCTs were chemotherapy trials.
Table 4. Nutrition Support.

<table>
<thead>
<tr>
<th>Disease Site (n)</th>
<th>% of Patients With Nutrition Support</th>
<th>% of Malnourished Patients With Nutrition Support</th>
<th>% of Non-Malnourished Patients With Nutrition Support</th>
<th>% Receiving Oral Supplements</th>
<th>% Receiving Enteral Nutrition</th>
<th>% Receiving Parenteral Nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood (377)</td>
<td>34.5</td>
<td>44.5</td>
<td>29.3</td>
<td>20.3</td>
<td>9.5</td>
<td>16.2</td>
</tr>
<tr>
<td>Head and neck (366)</td>
<td>63.7</td>
<td>76.5</td>
<td>51.3</td>
<td>36.4</td>
<td>40.4</td>
<td>6.1</td>
</tr>
<tr>
<td>Lung (247)</td>
<td>42.9</td>
<td>55.4</td>
<td>32.6</td>
<td>38.8</td>
<td>11.1</td>
<td>8.1</td>
</tr>
<tr>
<td>Breast (229)</td>
<td>14.8</td>
<td>34.0</td>
<td>9.89</td>
<td>12.3</td>
<td>5.2</td>
<td>4.1</td>
</tr>
<tr>
<td>Colon/rectum (191)</td>
<td>30.4</td>
<td>41.3</td>
<td>23.3</td>
<td>21.5</td>
<td>5.8</td>
<td>10.9</td>
</tr>
<tr>
<td>Esophagus/stomach (103)</td>
<td>65.0</td>
<td>77.4</td>
<td>46.3</td>
<td>47.8</td>
<td>25.8</td>
<td>19.6</td>
</tr>
<tr>
<td>Uterus/ovaries (87)</td>
<td>32.2</td>
<td>41.0</td>
<td>25.0</td>
<td>14.7</td>
<td>6.8</td>
<td>21.3</td>
</tr>
<tr>
<td>Prostate (72)</td>
<td>13.9</td>
<td>40.0</td>
<td>9.7</td>
<td>13.0</td>
<td>1.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Pancreas (42)</td>
<td>66.7</td>
<td>78.6</td>
<td>42.9</td>
<td>55.0</td>
<td>6.3</td>
<td>24.3</td>
</tr>
<tr>
<td>Kidney/bladder (29)</td>
<td>41.4</td>
<td>66.7</td>
<td>14.3</td>
<td>28.6</td>
<td>15.4</td>
<td>7.7</td>
</tr>
<tr>
<td>Others (160)</td>
<td>31.9</td>
<td>52.2</td>
<td>23.7</td>
<td>19.1</td>
<td>10.6</td>
<td>10.2</td>
</tr>
<tr>
<td>Total (1903)</td>
<td>39.8</td>
<td>57.6</td>
<td>28.4</td>
<td>24.2</td>
<td>13.8</td>
<td>9.6</td>
</tr>
</tbody>
</table>
Nutrition care in patients with cancer: A retrospective multicenter analysis of current practice - Indications for further studies?

(Drissi et al. Clin Nutr 2015;34:207)

Survey on 26561 oncologic pts

2.46% received PN (HPN 78%)

most frequent primaries: CR 21%, Stomach 16.5%, Pancreas 16%, Lung 10%

indications: GI impaired transit 15%, malabsorption 8.5%, other 81%
PN is recommended if there is a benefit

• Evidence of a «benefit»
  - what does «benefit» mean (objective vs subjective)
  - how do you measure it?

• Considerations of the cost: there may be small benefits at high cost (so-called low cost-effectiveness) when we are dealing with a treatment which does not represent the primary therapy
PN, a MEDICAL THERAPY and/or a BASIC TREATMENT?

**MEDICAL THERAPY**

- Drug is any chemical agent which affects living processes *(Goodman & Gilman 1941)*
- Physicians prescribe PN
- Physicians and medical societies consider nutrition as a therapy
- PN is a medical therapy for ill people
- It should be validated by RCT

**BASIC TREATMENT**

- Also “natural” nutrition affects living processes *(Paradoxically all humans got intrauterine PN)*
- Dietitians prescribe PN in USA and patients and relatives often ask for it
- Nourishment is viewed by the relatives as an act of love and care
- Nutrition is essential both to ill and healthy people
- It is ethically impossible to have a no-PN arm and hence a high level of evidence
...the ethics of clinical research requires a state of genuine uncertainty on the part of the clinical investigator or the expert medical community regarding the comparative therapeutic merits of each arm in a trial...
MAIN AREAS of INVESTIGATIONS CONCERNING PN in ONCOLOGY

1 PN as an adjunct to «curative» chemotherapy (*adjunctive PN*)

(PN mainly considered as a drug, administered regardless of the nutritional state, with nonnutritional objective end-points)

2 PN in «incurable» patients (*supportive PN*)

(PN mainly considered as a life-supporting treatment in starving patients often belonging to the palliative area)

- A: studies on objective nutritional /clinical end-points
- B: studies on subjective end-points (quality of life)
MAIN AREAS of INVESTIGATIONS CONCERNING PN in ONCOLOGY

1 PN as an adjunct to «curative» chemotherapy
   (PN mainly considered as a drug, administered regardless of the nutritional state, with
   nonnutritional objective end-points)

2 PN in «incurable» patients
   (PN mainly considered as a life-supporting treatment in starving patients often belonging to a
   palliative area)
   - A: studies on objective nutritional /clinical end-points
   - B: studies on subjective end-points (quality of life)
# EFFECTS of ADJUNCTIVE PN to ONCOLOGIC THERAPY

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>RCT</th>
<th>#PTS</th>
<th>NUTRITIONAL STATUS</th>
<th>TUMOUR</th>
<th>REGIMEN</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Cicco 1993</td>
<td>yes</td>
<td>53</td>
<td>mixed</td>
<td>mixed</td>
<td>35 - 1.5</td>
<td>Metabolic benefit in malnourished pts</td>
</tr>
<tr>
<td>Sikora 1998</td>
<td>no</td>
<td>45</td>
<td>?</td>
<td>esophagus</td>
<td>30/35 – 1.5</td>
<td>Better compliance with CT+RT</td>
</tr>
<tr>
<td>Scheid 2004</td>
<td>yes DB°</td>
<td>30</td>
<td>mixed</td>
<td>leukemia</td>
<td>≈29 - ?</td>
<td>Pts on Glut°°-PN (vs standard) had earlier neutrophil recovery</td>
</tr>
</tbody>
</table>

°DB=double blind; °°0.5g/Kg
In a patient undergoing curative anticancer drug treatment, if oral food intake is inadequate despite counselling and oral nutritional supplements (ONS), we recommend supplemental enteral or, if this is not sufficient or possible, parenteral nutrition

(Strong recommendation, evidence very low)
Radiotherapy: Use of parenteral nutrition
(ESPEN GL 2016)

We do not recommend parenteral nutrition as a general treatment in radiotherapy but only if adequate oral/enteral nutrition is not possible, e.g. in severe radiation enteritis or severe malabsorption

(Strong recommendation, evidence very low)
## EFFECTS of PN vs STANDARD REGIMENS in HCT

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>RCT</th>
<th>#PTS</th>
<th>OUTCOME</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weisdorf 1987</td>
<td>yes</td>
<td>137</td>
<td>PN vs standard iv infusion</td>
<td>PN better survival, engraftment, Los and GVHD</td>
</tr>
<tr>
<td>Geibic 1991</td>
<td>no</td>
<td>28</td>
<td>PN 1.6 vs 2 gAA/Kg</td>
<td>High AA better maintenance BW and LBM</td>
</tr>
<tr>
<td>Charuas 1997</td>
<td>DB°</td>
<td>258</td>
<td>PN vs standard iv infusion</td>
<td>PN better maintenance BW but later resumption of oral intake</td>
</tr>
<tr>
<td>Tavakoli-Ardanaki 2013</td>
<td>no</td>
<td>30</td>
<td>Personalized vs standard PN</td>
<td>pPN: ↓LoS ↓infections, ↓BW loss, ↓ptls and packed cells transfusions</td>
</tr>
</tbody>
</table>

*DB: DOUBLE BLIND
## EFFECTS OF PN vs EN in HCT

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>RCT</th>
<th># PTS</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Szeluga 1987</td>
<td>yes</td>
<td>57</td>
<td>PN more hyperglicemia, more CVC complications</td>
</tr>
<tr>
<td>Roberts 2003</td>
<td>yes</td>
<td>55</td>
<td>PN better nutrititional status and LBM</td>
</tr>
<tr>
<td>Guieze 2014</td>
<td>no</td>
<td>56</td>
<td>PN more fever episodes, more antifungal therapies, more transfers in ICU</td>
</tr>
</tbody>
</table>
High-dose chemotherapy and HCT: Enteral and parenteral nutrition
(ESPEN GL 2016)

If oral nutrition is inadequate we suggest preferring enteral tube feeding to parenteral nutrition, unless there is severe mucositis, intractable vomiting, ileus, severe malabsorption, protracted diarrhea or symptomatic gastrointestinal graft versus host disease (GvHD) (Strong recommendation, evidence low)
## RCTs of GLUTAMINE-ENRICHED PN vs PN in HCT

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>#PTS</th>
<th>Gln g/Kg</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziegler 1992</td>
<td>45</td>
<td>0.57</td>
<td>Less infections, shorter hospital stay</td>
</tr>
<tr>
<td>Schloerb 1993</td>
<td>29</td>
<td>0.73</td>
<td>No difference in clinical infection and mortality</td>
</tr>
<tr>
<td>Pytlik 2002</td>
<td>40</td>
<td>0.39</td>
<td>More mucositis, opioids, relapses, deaths and longer hospital stay</td>
</tr>
<tr>
<td>Sykorova 2005</td>
<td>44</td>
<td>0.40</td>
<td>Poorer overall, disease/event free-survival</td>
</tr>
<tr>
<td>Da Gama Torres 2008</td>
<td>53</td>
<td>0.40</td>
<td>Better survival at 100 and 180 days</td>
</tr>
<tr>
<td>Uderzo 2011</td>
<td>120</td>
<td>0.40</td>
<td>No difference in mucositis and clinical outcome</td>
</tr>
</tbody>
</table>
High-dose chemotherapy and HCT: Glutamine-enriched PN (ESPEN GL 2016)

There are insufficient consistent clinical data to recommend glutamine to improve clinical outcome in patients undergoing high-dose chemotherapy and hematopoetic stem cell transplantation. (Strong recommendation, evidence low)
MAIN AREAS of INVESTIGATIONS CONCERNING PN in ONCOLOGY

1 PN as an adjunct to «curative» chemotherapy
   (PN mainly considered as a drug, administered regardless of the nutritional state, with nonnutritional objective end-points)

2 PN in «incurable» patients
   (PN mainly considered as a life-supporting treatment in starving patients belonging to a palliative area)
   - A: studies on objective nutritional / clinical end-points
   - B: studies on subjective end-points (quality of life)
Supplemental Parenteral Nutrition

(Lundholm et al. 2004)

309 patients with progressive cachexia and receiving indomethacin, EPO and iron (when necessary) were randomized to HPN or no-HPN when oral intake dropped to 21-24 Kcal/Kg

At intention-to-treat basis: ↑ energy balance
As-treated analysis: ↑ energy balance
↑ survival
↑ maximum exercise capacity

Total AA intake g/Kg/d: ~ 0.8 (ent)+ 0.6-0.9 (iv)
Effects of PN support on BMI and BCM in patients with pancreatic cancer on chemotherapy

(Pelzer et al. 2010)

32 patients receiving PN (25kcal/kg/d, FAT >35% total energy, AA 1.2-1.5 g/kg/d for 18 weeks
Development and validation of a nomogram to predict survival in incurable cachectic cancer patients on home parenteral nutrition.

Bozzetti F1, Cotogni P2, Lo Vullo S3, Pironi L4, Giardiello D5, Mariani L5.

Author Information

Abstract

BACKGROUND: The use of home parenteral nutrition (HPN) in incurable cancer patients is extremely varied across different countries and institutions. In order to assess the clinical impact implied, we previously conducted a survey of incurable cancer patients receiving HPN, which shows that survival was markedly affected by Karnofsky performance status (KPS), tumor spread, Glasgow prognostic score (GPS) and tumor site. The aim of this study was to develop a nomogram incorporating the above factors for survival prediction.

PATIENTS AND METHODS: We gathered a series of 579 patients, all receiving HPN, which was randomly split into a training and a testing sample. Using Cox proportional hazard regression modeling, a nomogram was built in the training sample, in order to estimate median survival or survival probability at 3 and 6 months according to individual patient characteristics. The nomogram performance was then verified in the testing sample.

RESULTS: In the training sample, median survival was 3.2 (95% CI 3.0-3.7) months. GPS, KPS, tumor site and spread were confirmed to be significant prognostic factors. A significant interaction was also shown between the site and spread while weight loss (WL), adjusted for body mass index, failed to provide any substantial prognostic contribution. In the testing sample, nomogram performance was good in terms of calibration and discreet regarding discrimination.

CONCLUSION: With the growing availability of new oncological treatments and their tendency to transform the trajectory of the advanced cancer into a chronic condition characterized by progressive WL and poor nutrients intake, an increasing number of patients are expected to receive HPN. In such a setting, tools for predicting the survival outcome may play a role toward personalized medicine and for investigating novel experimental therapies. Our proposed nomogram is a step forward in this direction but needs to be made stronger in order to definitely have clinical utility.
Survival of 414 incurable cachectic (sub)obstructed cancer patients on HPN

(Bozzetti et al. Annals of Oncology 2014)

3-month: 57%   6-month: 28%
Six combinations of variables associated with ≥3-month survival

<table>
<thead>
<tr>
<th>Glasgow</th>
<th>Karnofsky</th>
<th>Survival ≥3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&gt;50</td>
<td>79%</td>
</tr>
<tr>
<td>0</td>
<td>Up to 50</td>
<td>61%</td>
</tr>
<tr>
<td>1</td>
<td>&gt;50</td>
<td>58%</td>
</tr>
<tr>
<td>2</td>
<td>&gt;50</td>
<td>55%</td>
</tr>
<tr>
<td>1</td>
<td>Up to 50</td>
<td>36%</td>
</tr>
<tr>
<td>2</td>
<td>Up to 50</td>
<td>31%</td>
</tr>
</tbody>
</table>
18 combinations of variables associated with ≥6-month survival

<table>
<thead>
<tr>
<th>Glasgow</th>
<th>Karnofsky</th>
<th>Locoregional</th>
<th>Metastatic</th>
<th>Both (LR)</th>
<th>≥6-mo survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&gt;50</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>51%</td>
</tr>
<tr>
<td>..........</td>
<td>............</td>
<td>..............</td>
<td>.............</td>
<td>............</td>
<td>................</td>
</tr>
<tr>
<td>2</td>
<td>Up to 50</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>5%</td>
</tr>
</tbody>
</table>

16 intermediate probabilities
The prognosis of incurable cachectic cancer patients on home parenteral nutrition: a multi-centre observational study with prospective follow-up of 414 patients


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Received 3 October 2012; revised 22 March and 19 July and 20 November 2013; accepted 20 November 2013

Background: The role of home parenteral nutrition (HPN) in incurable cachectic cancer patients unable to eat is extremely controversial. The aim of this study is to analyse which factors can influence the outcome.

Patients and methods: We studied prospectively 414 incurable cachectic (sub)obstructed cancer patients receiving HPN and analysed the association between patient or clinical characteristics and survival status.

Results: Median weight loss, versus pre-disease and last 6-month period, was 24% and 16%, respectively. Median body mass index was 19.5, median KPS was 60, median life expectancy was 3 months. Mean/Median survival was 4.7/3.0 months; 50.0% and 22.9% of patients survived 3 and 6 months, respectively. At the multivariable analysis, the variables significantly associated with 3- and 6-month survival were Glasgow Prognostic Score (GPS) and KPS, and GPS, KPS and tumour spread, respectively. By the aggregation of the significant variables, it was possible to dissect several classes of patients with different survival probabilities.

Conclusions: The outcome of cachectic incurable cancer patients on HPN is not homogeneous. It is possible to identify groups of patients with a ≥6-month survival (possibly longer than that allowed in starvation). The indications for HPN can be modulated on these clinical/biochemical indices.

Key words: cancer cachexia, home parenteral nutrition, incurable cancer patient, malignant obstruction
Figure 1. Cox modeling based nomogram for predicting 3-, 6-month and median OS. Instructions on how to use the nomogram for building survival estimates are supplied at the bottom of the Results section.
MAIN AREAS of INVESTIGATIONS CONCERNING PN in ONCOLOGY

1 PN as an adjunct to «curative» chemotherapy
(PN mainly considered as a drug, administered regardless of the nutritional state, with nonnutritional objective end-points)

2 PN in «incurable» patients
(PN mainly considered as a life-supporting treatment in starving patients belonging to a palliative area)
- A: studies on objective nutritional /clinical end-points
- B: studies on subjective end-points (quality of life)
SUBJECTIVE BENEFIT (QUALITY OF LIFE)

QoL is a reflection of the difference at a given time between the hopes and the expectations of an individual and the individual’s present experience (*Calman 1984*). However consider that:

1. Different individuals have different expectations
2. Expectations may change over time
3. Individuals may be at different time points in the trajectory of their illness when measurement of QoL are made
# HPN and QUALITY of LIFE in MALNOURISHED ADVANCED CANCER PATIENTS

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>ßPTS</th>
<th>ONCOLOGIC THERAPY</th>
<th>METHODS</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bozzetti 2002</td>
<td>69</td>
<td>No, incurable pts</td>
<td>Rotterdam Symptom Checklist, every mo till death</td>
<td>QoL scores stable till 2-3 mos before death</td>
</tr>
<tr>
<td>Culine 2013</td>
<td>437</td>
<td>yes</td>
<td>FACT-G day 1 and 28</td>
<td>↑physical, functional, emotional, familial/social status</td>
</tr>
<tr>
<td>Vashi 2014</td>
<td>52</td>
<td>yes</td>
<td>EORTC QLQ-C30</td>
<td>↑Global QoL index at 1-3 mos</td>
</tr>
<tr>
<td>Cotogni 2016</td>
<td>111</td>
<td>yes 2/3</td>
<td>EORTC QLQ-C30 every mo till death or weaning from HPN</td>
<td>↑Global QoL index and physical, role, emotional functioning more evident in pts on oncologic therapy</td>
</tr>
</tbody>
</table>

In all studies except Bozzetti, HPN was «supplemental»
We recommend offering and implementing nutritional interventions in patients with advanced cancer only after considering together with the patient the prognosis of the malignant disease and both the expected benefit on quality of life and potentially survival as well as the burden associated with nutritional care (Strong recommendation, low evidence)
CONCLUSION

• Few RCTs support the indications for PN in cancer patients

• Most of the recommendations rely on the awareness that malnutrition and chronic starvation furtherly worsen the general status, compliance with oncologic therapy (and its effectiveness), quality of life and finally outcome. The level of evidence is usually low

• Although the usual recommendation is to administer PN only when oral/enteral nutrition is not possible, one should consider some potential benefits of PN also in some patients with working gut
SOME ADVANTAGES of PN vs TUBE FEEDING

- Patients may prefer PN°
- Compliance may be better (many patients already harbour a CVC)
- PN is more «passive» whereas EN is more «forced»
- Better modulation of substrates
- The regimen may be adjusted without withdrawing nutritional support
- 600-ml bags containing 600 npKcal and 35 g AA (to be delivered in about 8 hrs) are available in the market

°Scolapio 2002
Federico Bozzetti gave independent lectures at scientific and educational events sponsored by nutritional industries. There is no conflict of interest.