

SUPPORTIVE CARE

ESMO preceptorship on Advanced non resectable hepatocellular carcinoma, biliary and pancreatic cancer

Karin Jordan

Friday, 6 December 2019





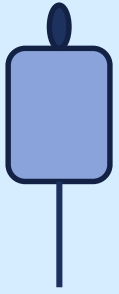
DISCLOSURES

Karin Jordan

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Chemo-therapy

Radio-therapy



BENEFIT

Overall Survival

Progression-free Survival

RISK

- Muscular Disorders
- Thrombocytopenia
- Constipation
- Infection
- Fertility
- Malnutrition
- Anemia
- Lymphedema
- Sexual Dysfunction
- Anorexia
- Lung toxicity
- Osteoporosis
- Ototoxicity
- Immune-related Toxicity
- Paravasation
- Pain
- Fatigue
- Nausea
- Allergic Reaction
- Venous Thromboembolism
- Rash
- Alopecia
- Vomiting
- Cardiotoxicity
- Central nervous Toxicity
- Neurotoxicity
- Xerostomia
- Psychological problems
- Skin toxicity
- Diarrhoea
- Mucositis
- Hot flashes
- Vascular disorders
- Tumorlysis
- Renal Toxicity
- Osseous Complications
- Taste alteration
- Psychiatric disorders
- Neutropenia

SPECIAL ARTICLE

European Society for Medical Oncology (ESMO) position paper on supportive and palliative care

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**Focus on all different aspects on supportive and palliative care
„Patient Centred Care“**

Key Patient-centred care interventions - Assessment, Monitoring and Management

Table 1. Key patient-centred care interventions (examples)

Assessment

Monitoring and intervention:
regular changes in patients' health status preferably assessed with PROMs or other validated assessment tools

Management of cancer-related symptoms and other needs

Management of anticancer treatment-related toxicities and complications, including prevention

Strictly to be avoided

e.g. with PRO

- Monitoring of adverse events
- Coping mechanisms

- Management of PNP, CINV, Pain, ...
- Coping with life limiting expectancies



PRO: Patient reported outcome
 PNP: Polyneuropathy
 CINV: Chemotherapy induced nausea and vomiting

FOLFIRINOX IN ADVANCED PANCREATIC CANCER

Incidence of adverse events (all grades (%)) / grade 3-4 (%))

	Boone 2013 J Surg Oncol	Conroy 2005 J Clin Oncol	Conroy 2011 N Engl J Med	Faris 2013 Oncologist	Hosein 2012 BMC Cancer	Marthey 2014 Ann Surg Oncol	Moorcraft 2014 Clin Col. Canc.	Peddi 2012 JOP
Number of patients	21	46	171	22	18	77	49	61
Abdominal pain	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A./ 8,2
Alopecia	N.A.	N.A.	N.A.	N.A.	67 / 0	12 / 0	N.A.	N.A.
Anemia	N.A.	N.A./ 18	N.A./7,8	100 / 0	72 / 11	34 / 1	57 / 4	N.A.
Anorexia	N.A.	N.A.	N.A.	N.A.	22 / 0	N.A.	N.A.	N.A.
Diarrhea	0 / 5	N.A./ 17	N.A./12,7	N.A.	33 / 11	40 / 6	37 / 4	N.A./ 3,3
Elevated ALT/AST	N.A.	64 / 9	N.A./7,3	N.A.	N.A.	N.A.	N.A.	N.A.
Febrile Neutropenia	N.A.	N.A.	N.A./5,4	N.A.	0 / 17	N.A.	0 / 14	N.A./ 4,9
Fatigue	5 / 0	N.A./ 22	N.A./23,6	N.A.	78 / 11	29 / 6	56 / 18	N.A./ 4,9
Hand-foot-Syndrome	N.A.	N.A.	N.A.	N.A.	N.A.	1 / 0	N.A.	N.A.
Hospitalisation	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	34,4
Leucopenia	14 / 10	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Mucositis	N.A.	N.A.	N.A.	N.A.	11 / 0	5 / 0	18 / 4	N.A.
Nausea	10 / 0	N.A./ 20	N.A.	N.A.	50 / 0	N.A.	28 / 1	N.A.
Neutropenia	5 / 15	N.A./ 52	N.A./45,7	9 / 18	33 / 22	23 / 11	26 / 29	N.A./ 19,7
Neuropathy	0 / 5	N.A./ 15	N.A./9,0	N.A.	33 / 0	47 / 4	51 / 4	N.A.
Thromboemb. Events	0 / 5	N.A.	N.A./6,6	5	N.A.	N.A.	2 / 12	N.A.
Thrombocytopenia	10 / 10	N.A./ 6	N.A./ 9,1	77 / 5	44 / 17	24 / 0	39 / 10	N.A./ 3,3
Vomiting	10 / 0	N.A./ 17	N.A./14,5	N.A.	N.A.	43 / 9	10 / 4	N.A.
Weight loss	5 / 5	N.A.	N.A.	N.A.	11 / 0	N.A.	N.A.	N.A.

Sign in

How can we help you ?

SEARCH

About Us | **Membership** | **Guidelines** | **Conferences** | **Career Development** | **Research** | **Patients** | **Policy** | **OncologyPRO**

- Guidelines News
- ESMO Guidelines Slide Sets
- Breast Cancer
- Cancers of Unknown Primary Site
- Endocrine and Neuroendocrine C...
- Gastrointestinal Cancers
- Genitourinary Cancers
- Gynaecological Cancers
- Haematological Malignancies
- Head and Neck Cancers
- Hereditary Syndromes
- Lung and Chest Tumours
- Melanoma
- Neuro-Oncology
- Sarcoma and GIST
- Supportive and Palliative Care
- ESMO-MCBS
- Pocket Guidelines & Mobile App
- ESMO Guidelines Methodology

Neuroendocrine Cancers

Gastrointestinal Cancers

Genitourinary Cancers

Establishing the highest standards of clinical practice is a collective effort of the whole oncology community. The ESMO Clinical Practice Guidelines, prepared and reviewed by leading experts, help you provide patients with the best care options.

Cancer research is constantly advancing. Evidence-based medicine transfers the results of that re-

➤ **Free Download from ESMO Webpage**

<https://www.esmo.org/Guidelines/Supportive-and-Palliative-Care>

ESMO Clinical Practice Guidelines Supportive and Palliative Care 2017 / 2018

Management of Cancer Pain in Adult Patients: ESMO Clinical Practice Guidelines	M. Fallon, 2018
Diagnosis, Assessment and Management of Constipation in Advanced Cancer: ESMO Clinical Practice Guidelines	P.J. Larkin, 2018
Diarrhoea in Adult Cancer Patients: ESMO Clinical Practice Guidelines	P. Bossi, 2018
Management of Anaemia and Iron Deficiency in Patients With Cancer: ESMO Clinical Practice Guidelines	M. Aapro, 2018
Management of Infusion Reactions to Systemic Anticancer Therapy: ESMO Clinical Practice Guidelines	S. Roselló, 2017
Management of Toxicities from Immunotherapy : ESMO Clinical Practice Guidelines	J. Haanen, 2017
MASCC and ESMO Consensus Guidelines for the Prevention of Chemotherapy and Radiotherapy-Induced Nausea and Vomiting : ESMO Clinical Practice Guidelines	F. Roila, 2016
Management of Febrile Neutropenia : ESMO Clinical Practice Guidelines	J. Klastersky, 2016

ANTIEMESIS

Supportive Care in Pancreatic and HPB malignancies

ANTIEMETIC AGENTS

Class	Drug examples	Mode of action	Predominant efficacy	
			Acute	Delayed
5-HT ₃ rec.- antagonists	Ondansetron, Tropisetron, Granisetron, Palonosetron ("PA")	5-HT ₃ receptor	++ ++ ++ ++	+/- +/- +/- +
NK ₁ rec.-antagonists	Aprepitant, Fosaprepitant, Netupitant ("NE"), Rolapitant	NK ₁ receptor	+	++
Steroids	Dexamethasone	Multiple	+	+
Benzamides	Metoclopramide	DA D ₂ /5HT ₃ receptor	(+)	(+)
Benzodiazepines	GABA-chloride channel complex	GABA-chloride channel complex	(+)	(+)
Classical Neuroleptics	Haloperidol	Mainly D ₂ receptor	(+)	(+)
Atypical neuroleptics	Olanzapine	Multiple receptors*	+	+
Cannabinoids	Dronabinol, nabilone	CB1-Receptor Agonism, (CB2-Receptor)	(+)	(+)
Antihistamines	Diphenhydramine, hydroxyzine	Muscarinic/ cholinergic receptor	-	-
Ginger	Ginger	At least: 5-HT ₃ receptor	(+)	(+)

*(D1, D2, D3, D4), serotonergic (5-HT_{2A}, 5-HT_{2C}, 5-HT₃, 5-HT₆), adrenergic (α₁), histaminergic, (H₁), and muscarinic (m₁, m₂, m₃, m₄)

EMETOGENIC RISK OF I.V. AGENTS

High (> 90 %)	Cisplatin, Streptozocin, Carmustin, Dacarbazin, Antrazyclin/Cyclophosphamid based regimen, Cyclophosphamid ≥ 1500 mg/m ² , Mechlorethamin
Moderate (30-90 %)	Alemtuzumab, Arsentrioxide, Azacitidin, Bendamustin, Carboplatin, Clofarabin, Cyclophosphamid < 1500 mg/m ² , Cytarabin > 1000 mg/m ² , Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Ifosfamid, Interferon α , Irinotecan, Oxaliplatin, Romidepsin, Temozolomid, Thiotepa, Trabectedin
Low (10-30 %)	Aflibercept, Asparaginsäure, Belinostat, Blinatumomab, Bortezomib, Brentuximab, Cabazitaxel, Cetuximab, Cytarabin < 1000 mg/m ² , Dactinomycin, Docetaxel, Doxorubicin (liposomalpegyliert), Eribulin, Etoposid, 5-Fluorouracil, Gemcitabin, Ipilimumab, Methotrexat, Mitomycin, Nab-Paclitaxel, Paclitaxel, Panitumumab, Pemetrexed, Pertuzumab, Topotecan
Minimal (< 10 %)	Bevacizumab, Bleomycin, Buserelin, Busulfan, 2- Chlordeoxyadenosin, Cladribin, Fludarabin, Fulvestrant, Goserelin, Leuprorelin, Nivolumab, Pembrolizumab, Rituximab, Trastuzumab, Vinblastin, Vincristin, Vinorelbin

STATE OF THE ART

MASCC/ESMO & ASCO Guidelines („the easy way“)

	Antiemetics Acute Nausea and Vomiting	Antiemetics Delayed Nausea and Vomiting
High (> 90 %)	5-HT ₃ + DEX + NK ₁ + (OLA)*	DEX +**APR + (OLA)*
Moderate (30-90 %)	5-HT ₃ + DEX + NK ₁	No or** APR
	5-HT ₃ + DEX	No routine prophylaxis
Low (10-30 %)	5-HT ₃ or DEX or DOP	No routine prophylaxis
Minimal (< 10 %)	No routine prophylaxis	No routine prophylaxis

5-HT₃: Serotonin₃-Receptorantagonist, DEX: Dexamethasone, NK₁: Neurokinin₁-Receptorantagonist, DOP: Dopaminreceptorantagonist, OLA: Olanzapin

*In patients treated with highly emetogenic chemotherapy olanzapine may be considered with a 5-HT₃-RA plus dexamethasone, plus an NK₁-RA (MASCC/ESMO guideline Update 2017). In the ASCO guidelines Olanzapine is recommended in this setting.

**If APR 125 mg for acute, otherwise no NK₁-RA is necessary on day 2 and 3.



MUCOSITIS

Supportive Care in Pancreatic and HPB malignancies

STAGING AND RISK ASSESSMENT

National Cancer Institute Common Terminology Criteria for Adverse events Version 4.03

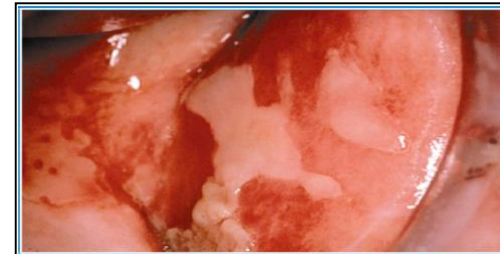
Grade 1	Asymptomatic or mild symptoms; intervention not indicated
Grade 2	Moderate pain; not interfering with oral intake; modified diet indicated
Grade 3	Severe pain; interfering with oral intake
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death



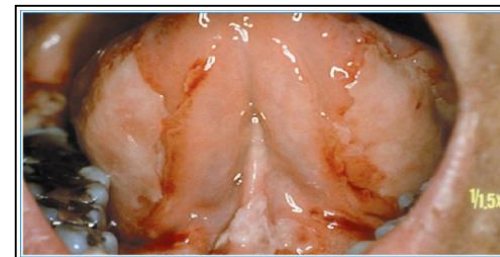
Grade 1



Grade 2



Grade 3



Grade 4

MOUTHWASH

What is recommended?

Prophylactical measure:

- Bolus 5-Fluorouracil Chemotherapy:
30 min of **oral cryotherapy (II)**.
- Mouthwash with plain water or 0.9 % NaCl¹



¹Leitlinienprogramm Onkologie: Supportive Therapie bei onkologischen PatientInnen – Langversion 1.0, 2016. AWMF Registernummer: 032/054OL

²Peterson et al. Ann Oncol (2015); 26:v139-151

PAINFUL MUCOSITIS

What is new?



- Mouthwash with Morphin 0.2 % (0, 2b) or Doxepin 0.5 % (0, 4) is recommended^{1,2,3}

Evidence for Doxepin mouthwash:

- RCT, crossover, n = 155, primary endpoint: pain reduction² and RCT, n=257³
- Doxepin versus placebo²; Doxepin vs. Diphenhydramine-lidocaine-antacide mouthwash³
- **Result: Clinically relevant pain reduction by doxepin mouthwash, but slightly more adverse events^{2,3}**

¹Leitlinienprogramm Onkologie: Supportive Therapie bei onkologischen PatientInnen – Langversion 1.0, 2016. AWMF Registernummer: 032/054OL

²Leenstra, J. L., et al. (2014) J Clin Oncol 32(15): 1571-1577, ³Sio T (2019) JAMA 321:1482-90.

SKIN TOXICITIES

Supportive Care in Pancreatic and HPB malignancies

HAND-FOOT-SYNDROME

Prophylaxis



MUST

Treatment of hyperkeratoses / fungal infections (A, LoE 5)

Pressure relief (comfortable shoes, avoidance of friction, and heat) (A, LoE 5)

SHOULD

Intensive skin care of hands and feet (Urea hand and foot cream/ ointment, for example Eucerin® 10 %) (B, LoE 1b)

CAN

Cooling hand and foot during infusion with Docetaxel (0, LoE 2b)

HAND-FOOT-SYNDROME

Treatment

- *Pressure relief (comfortable shoes, avoidance of friction, and heat) (A, LoE 5)*
- *Intensive skin care of hands and feet (Urea hand and foot cream/ ointment, for example Eucerin® 10 %) (B, LoE 1b)*
- *Cooling hand and foot during infusion with Docetaxel (0, LoE 2b)*

+ HFS ≥ grade 3:

MUST: Dose reduction/ enlargement of therapy intervals adapted to substance (A, LoE 5)

SHOULD: Topical Steroids (B, LoE 5)

CAN: Hydrocolloid dressing plantar (0, LoE 2b)

RASH

Prophylaxis



MUST

Basic therapy under EGFR inhibition (A, LoE 5)

(avoiding mechanical ,chemical noxes, UV-protection, ph-neutral skin-care, urea-containing cream)

SHOULD

Prophylactic administration of tetracyclines* to reduce the severity of acneiform exanthema (B- LoE 1b)

* Minocycline 2x50 mg/day or Doxycycline 2 x 100 mg / day
The most often used schema in studies were 8 weeks

CAN/ CANNOT

No recommendation for or against the use of topical steroids (0, LoE <2)



RASH Therapy

Depending on the severity of the acneiform exanthema

CTCAE grade 1:

SHOULD Basic therapy including oral antibiotics

Topical treatment with antibiotic-containing cream 2x/d (e.g. metronidazole, nadifloxacin), **(B, LoE 5)**

CTCAE grade 2:

SHOULD Therapy as for CTCAE grade 1, Topical steroids class 2-3 (prednicarbate), **(B, LoE 5)**

CTCAE grade 3/4:

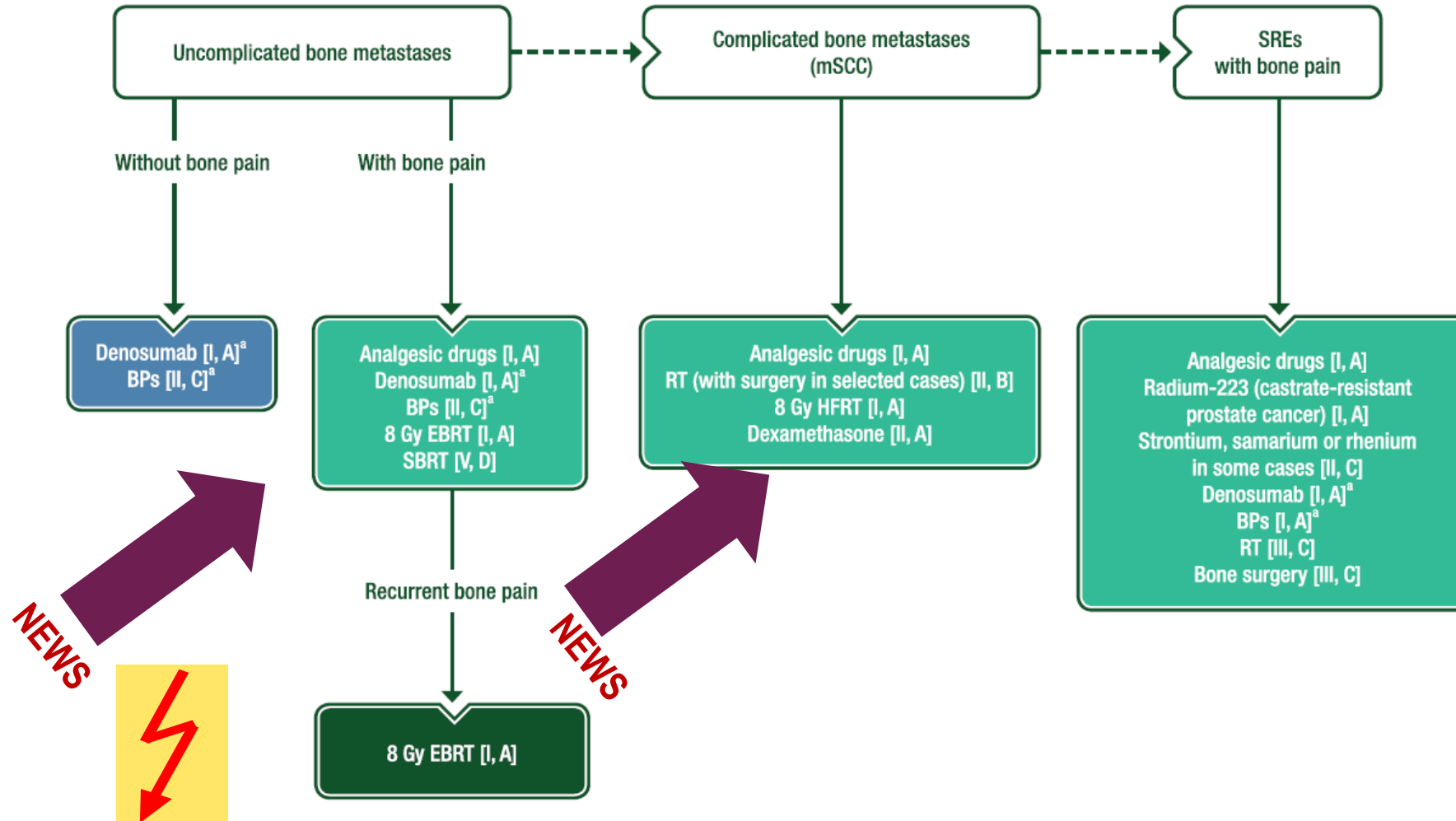
SHOULD Therapy as for CTCAE grade 2, Systemic glucocorticoids, Systemic antibiotic therapy

Possibly isotretinoin (CAVE: never in combination with systemic antibiotics, danger of brain edema!) **(B, LoE 5)**

BONE COMPLICATIONS

Supportive Care in Pancreatic and HPB malignancies

TREATMENT OF BONE PAIN DUE TO METASTASIS



^aPreventive dental measures are necessary before starting administration [III, A].

BP, biphosphonate; EBRT, external beam radiotherapy; HFRT, hypofractionated radiotherapy; mSCC, metastatic spinal cord compression; RT, radiotherapy; SBRT, stereotactic body radiotherapy; SRE, skeletal-related event.

“NEWS” – STATE OF THE ART



SRE: skeletal related event

Bisphosphonates – Dosing Interval - SRE

Every 4 weeks or every 12 weeks (after 1 year of 4 weeks intervall)? **option.**²

 **Every 12 weeks is not inferior**¹

Radiation for Spinal Cord Compression

SCORAD III, > 40 centers, n = 688, 20 Gy in 5 fractions versus 8 Gy once

 **Regarding the short lifetime of patients the single dose radiation seems to be the preferred**

¹Hortobagyi GN. et al., JAMA Oncol. 2017, Amadori, Aglietta et al. 2013, Ibrahim, Mazzarello et al. 2015

²Hoskin, P. et al., J Clin Oncol. 2017; 35(15_suppl): LBA100004

NEUROTOXICITY

Supportive Care in Pancreatic and HPB malignancies

PERIPHERAL NEUROPATHY

State of the Art

Prophylaxis

- Drugs: ☹️
- Exercise therapy: yes, can help
- Cryo- or Compression-therapy: Study 36¹, 42² Patients: Yes. Study > 100³ Patients: No




Therapy (consider: only plus symptoms can be treated):

- Drugs: **Duloxetine** (30 mg/d, week 1, followed by 60 mg/d (120 mg possible); less evidence: Gabapentin/Pregabalin, TriA: e.g. Amitriptylin
- Local: Baclofen/Amitriptylin/Ketamin (BAK), menthol cream (1 %), capsaicin 8 %
- Exercise therapy: sensomotoric training, increasing evidence



SPINAL CORD COMPRESSION – STATE OF THE ART –

„Updated Evidence Based Review“

- **Incidence:** 2.5 % - 5 % of tumor patients with non-curative intent
- **Dexamethasone:** 10 mg i.v. as an initial bolus, then 4-6 mg i.v. every 6 hours, over 2 weeks
- **Pain:**
 - Opiate
 - Gabapentin: 100-400 mg 3x daily (daily dose 600-1200 mg)
 - Pregabalin: 7.5 mg 2x daily
 - Amitriptylin or Nortriptylin: 10-25 mg each at night
- **Bone pain:** Bisphosphonates (maximum effect after 4 weeks)
- **Surgery / Radiotherapy / Both:**  Interdisciplinary decision, factors: spine stability, neurological deficit, prognosis

PAIN

Supportive Care in Pancreatic and HPB malignancies

CLINICAL PRACTICE GUIDELINES

Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines[†]

M. Fallon¹, R. Giusti², F. Aielli³, P. Hoskin⁴, R. Rolke⁵, M. Sharma⁶ & C. I. Ripamonti⁷, on behalf of the ESMO Guidelines Committee*



26 pages

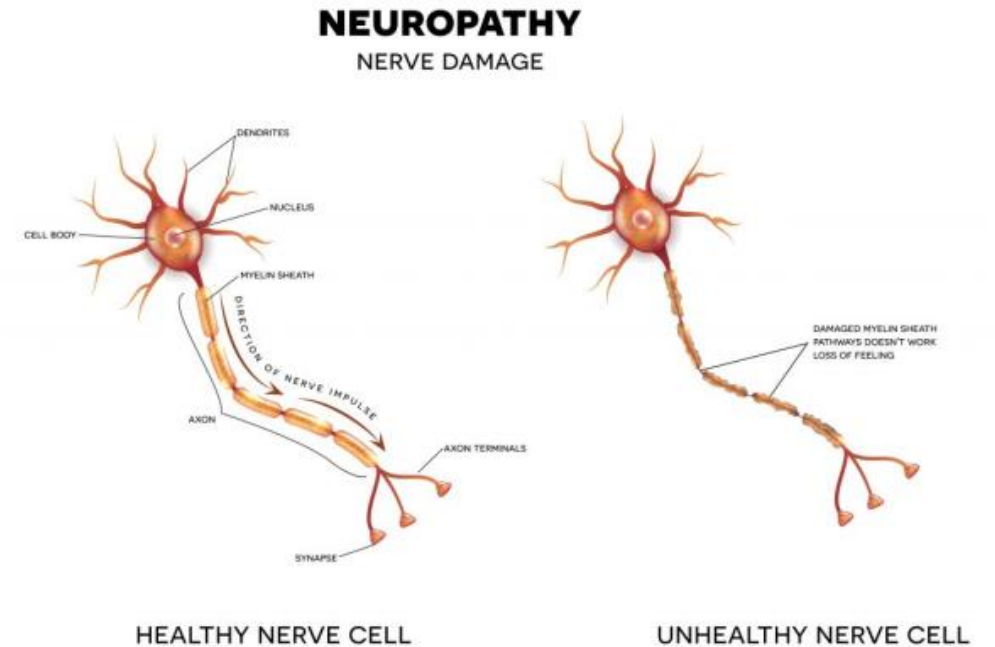
ASSESSMENT OF PAIN TO IMPROVE CHOICE OF THERAPY

Nociceptive (ongoing tissue damage)

- Somatic (e.g. bone pain)
- Visceral (e.g. gut or hepatic pain)

Neuropathic

- Damage or dysfunction in the nervous system (e.g. brachial plexopathy or spinal cord compression)



PRACTICAL APPROACH: PAIN ASSESSMENT TOOL

1. „What has been your worst pain in the last 24 h on a scale 0-10“
2. Monitor if the pain is < 3
3. More detailed assessment if the pain is > 3
4. Appropriate analgesic and monitor analgesic side effects

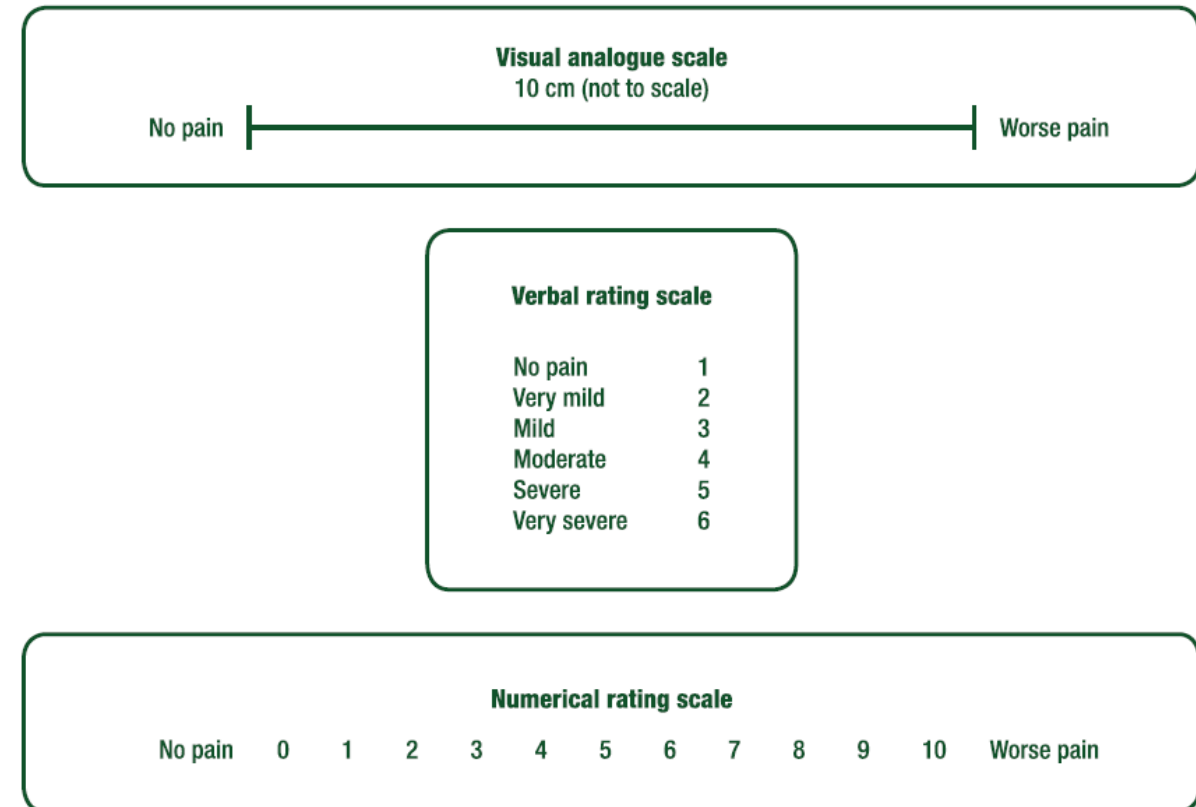
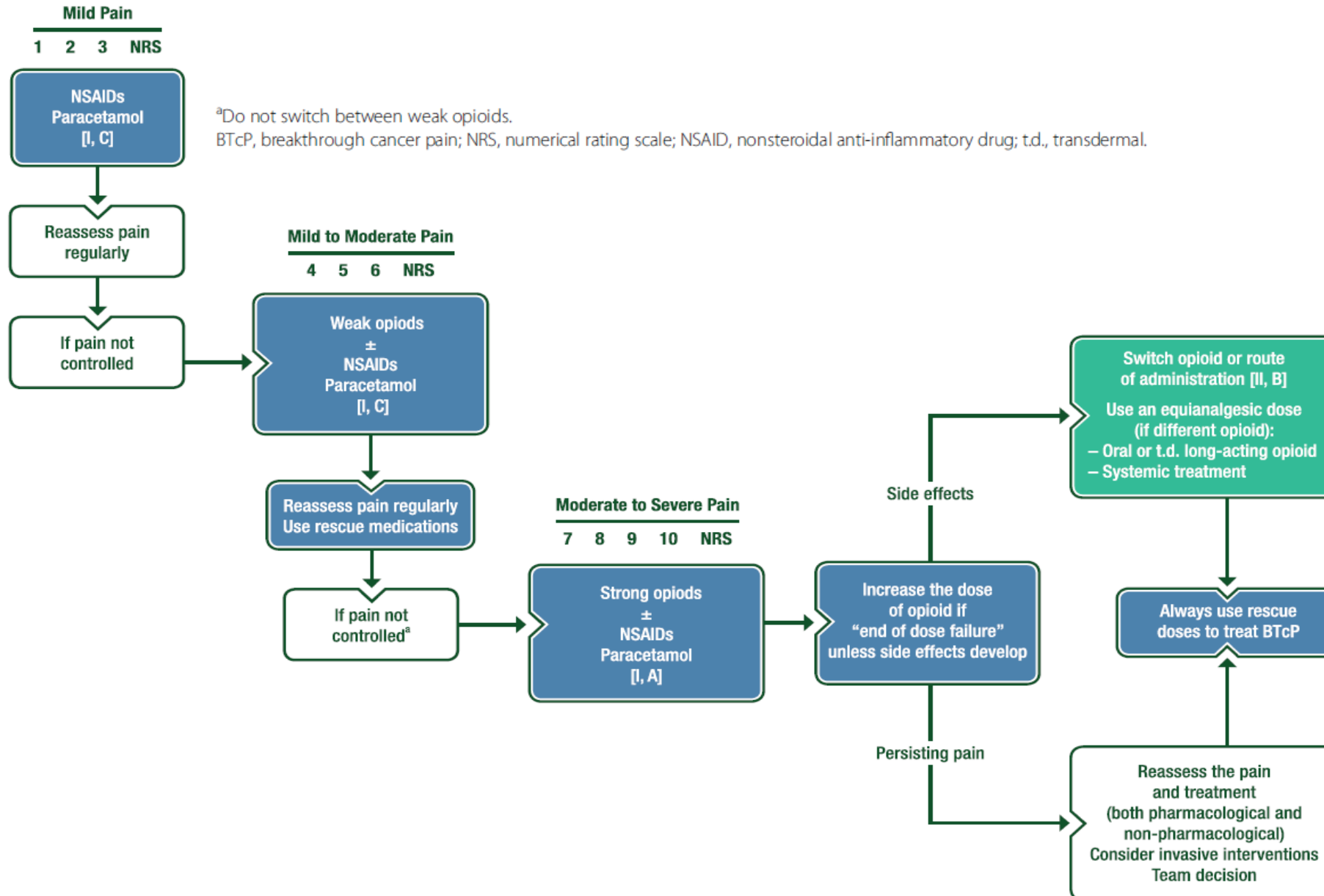


Figure 1. Validated and most frequently used pain assessment tools.

ESMO GUIDELINE: TREATMENT OF CANCER PAIN



RELATIVE ANALGESIC RATIOS FOR OPIOID SWITCHING

Table 3. Relative analgesic ratios for opioid switching

Opioids	Analgesic ratio	LoE	GoR	Evaluated studies (N)	References
Oral morphine to oral oxycodone	1:1.5	II	B	RCTs (4); PCT (2)	[69–74]
Oral oxycodone to oral hydromorphone	1:4	II	B	RCT (1)	[75]
Oral morphine to t.d. buprenorphine ^a	75:1	IV	C	PCT (1)	[76]
Oral morphine to t.d. fentanyl ^b	100:1	III	B	PCT (4)	[77–80]
Oral morphine to oral methadone	1:5 to 1:12	III	B	PCT (6)	[61, 62, 76, 81–83]
Oral morphine to oral hydromorphone	1:5 to 1:7.5	II	B	RCT (1)	[84]

^aExample: 60 mg oral morphine to 35 µg/h t.d. buprenorphine (equivalent to 0.8 mg/24 h).

^bExample: 60 mg oral morphine to 25 µg/h t.d. fentanyl (equivalent to 0.6 mg/24 h).

GoR, grade of recommendation; LoE, level of evidence; PCT, uncontrolled prospective cohort trial; RCT, randomised controlled trial; t.d., transdermal.

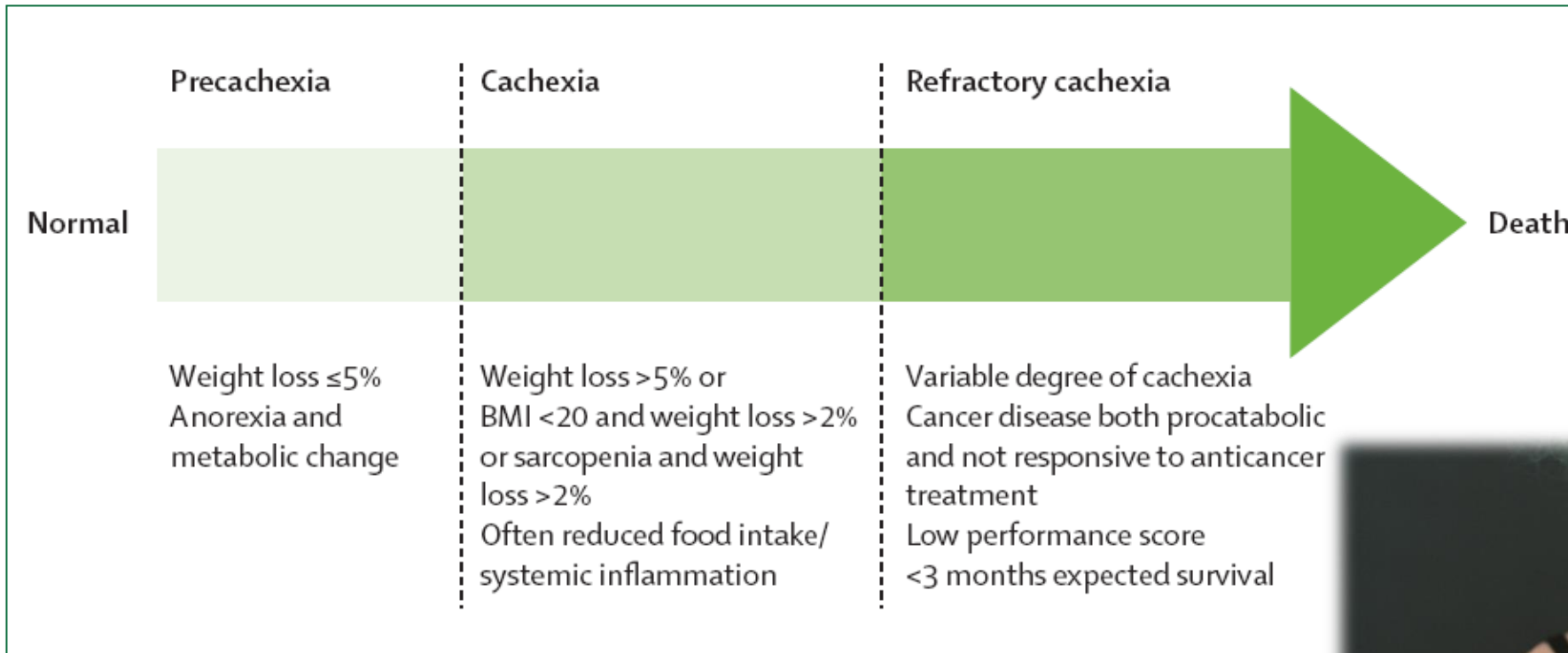
Adapted from [68] with permission.

CACHEXIA

Supportive Care in Pancreatic and HPB malignancies

CANCER CACHEXIA

Definition

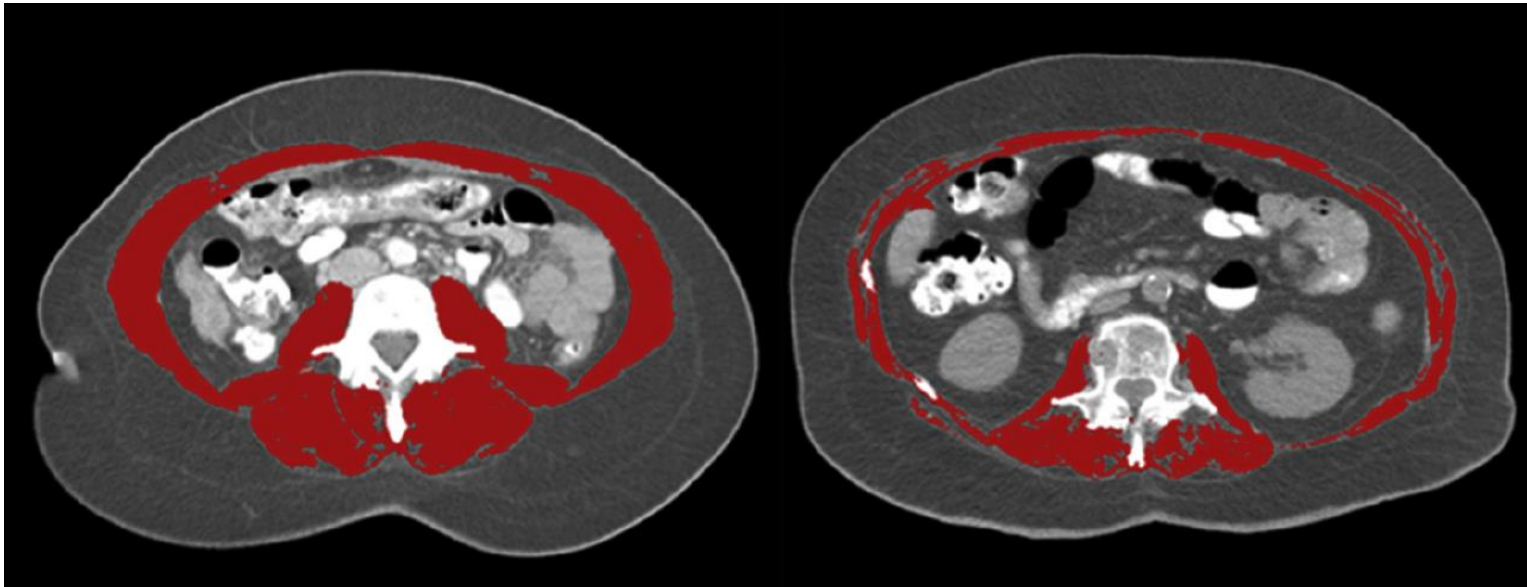


The patient does not necessarily have to be “skin and bones”!



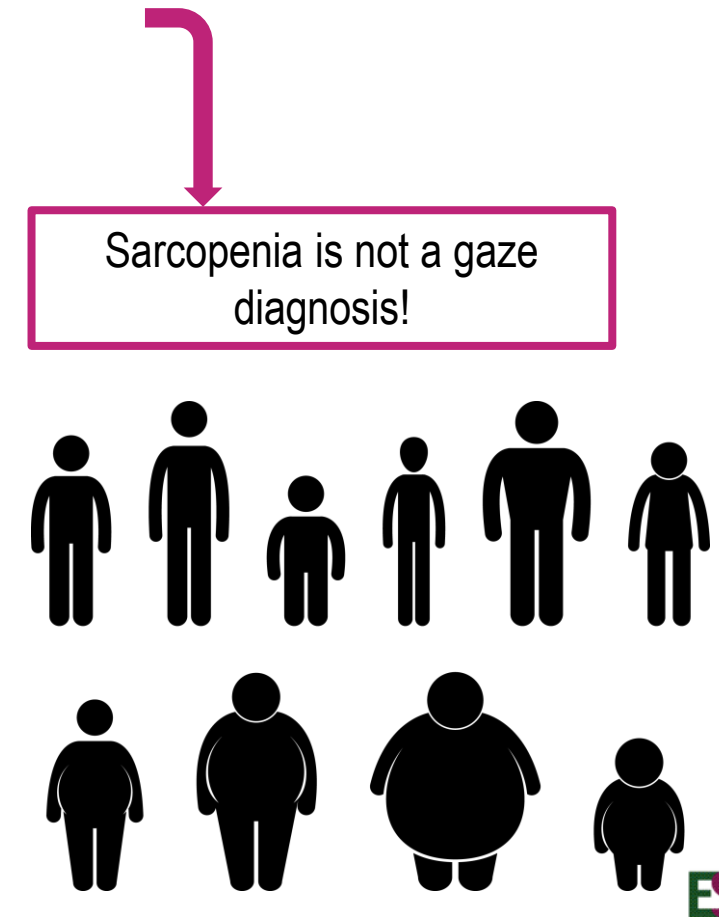
SARCOPENIA AND SARCOPENIC OBESITY

The loss of muscle mass is independent of the fat mass or body weight of a patient



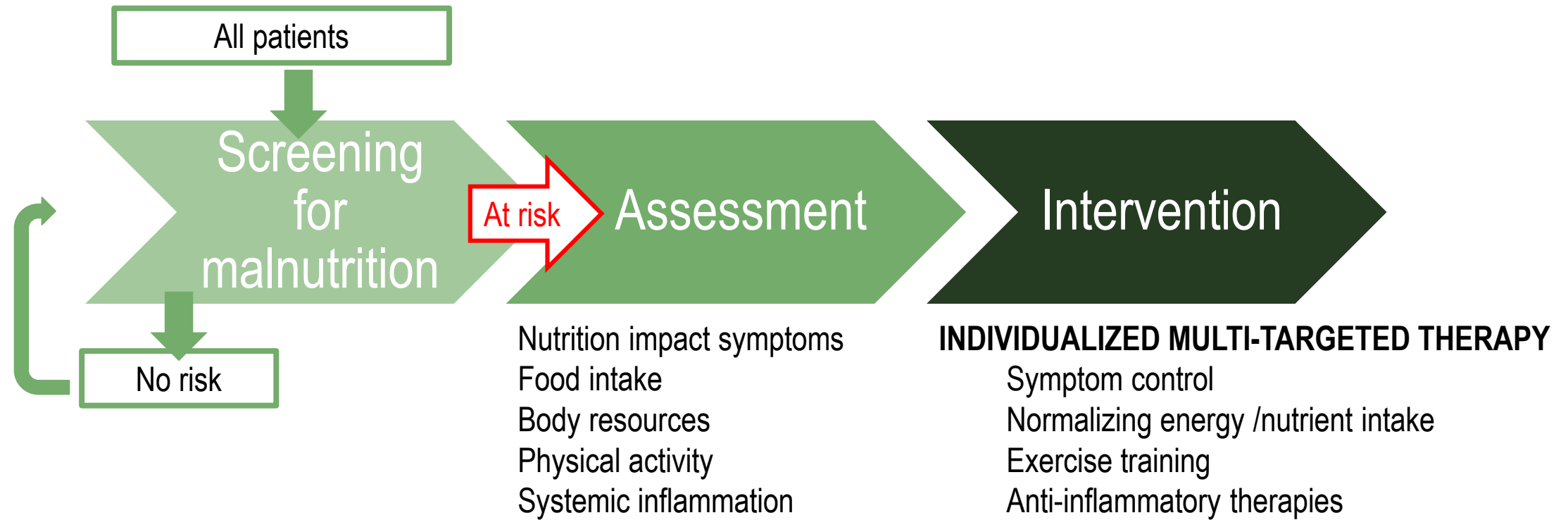
Normal vs. sarcopenic cancer patient, female, BMI: 26 kg/m²

Shachar SS et al., Eur J Cancer 57 (2016) 58-67



CACHEXIA, SARCOPENIA, SARCOPENIC OBESITY

What do we have to do?



ESPEN GUIDELINES ON NUTRITION IN CANCER PATIENTS

What do we have to do?

Energy and Nutrient Requirements (Recommendation grade)	
Energy	25-30 kcal/kg (STRONG)
Protein	1,0-1,5 g/kg (WEAK)
Vitamins/ Trace elements	Recommended daily ammount (STRONG)



Exercise

Maintain or increase level of physical activity (STRONG)

Pharmacologic Agents and Pharmaconutrition	
Anorexia	Corticosteroids or Progestins, watch for: side effects (WEAK)
Taste alterations	Cannabinoids (--)
Muscle Mass	Androgens (--)
Fat Free Mass	Amino acids/Metabolites (--)
Weight loss	NSAID (--)
Weight loss	EPA (N-3 fatty acids): 1.5 g/d or more (WEAK)
Early satiety	Metoclopramide, Domperidone (WEAK)

← Only in palliative settings!

EXERCISE

Supportive Care in Pancreatic and HPB malignancies

EXERCISE AND PHYSICAL ACTIVITY

What do we know by now?

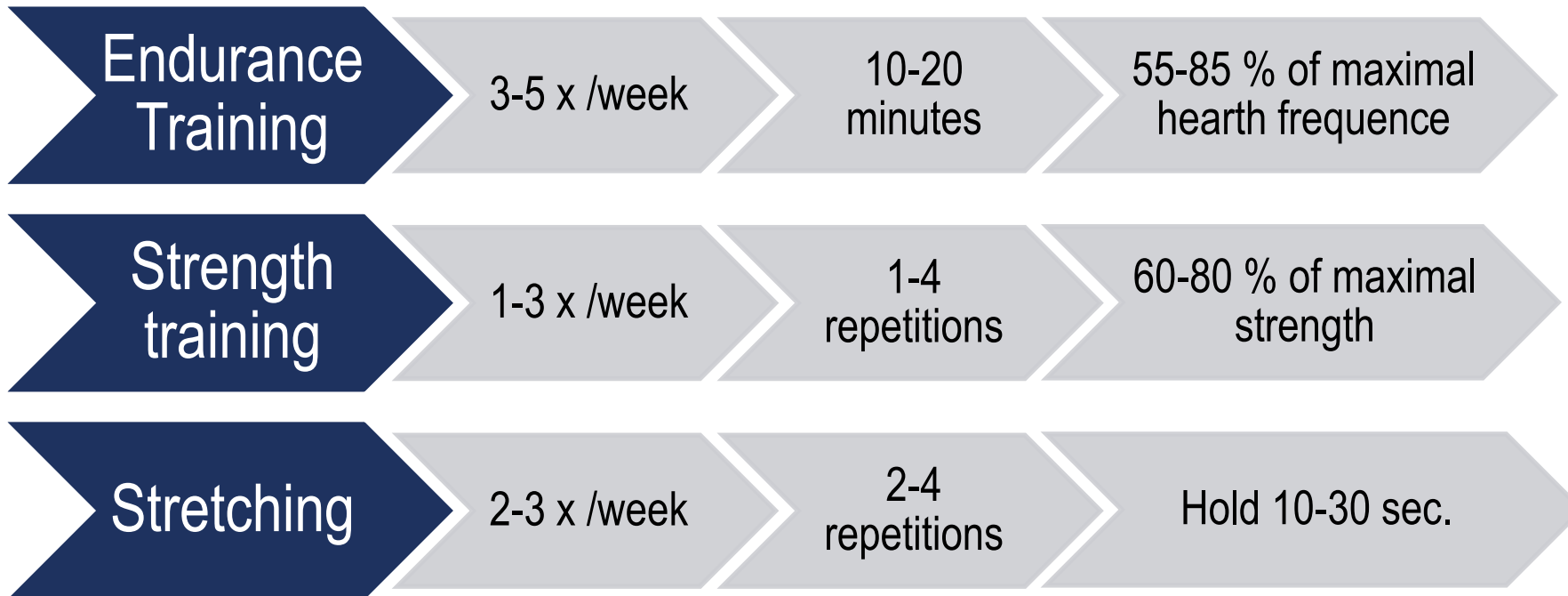
- . Reduction of treatment-related side effects
 - . Pain
 - . Nausea and vomiting
 - . Polyneuropathy
 - . Fatigue
- . Improvement of self-esteem and quality of life



**Exercise and Cancer
– Important and
effective!**

EXERCISE AND PHYSICAL ACTIVITY

What is recommended?



FATIGUE

Supportive Care in Pancreatic and HPB malignancies

STATE OF THE ART

Screening, Assessment and Management of Fatigue

Therapeutic approaches

- Therapy of accompanying factors (depression, anemia, ...)
- Physical activity (**more effective than drug interventions**)
- Pharmacological intervention
- "Mind Body Intervention"
- Psychosocial intervention

FATIGUE

Exercise is highly recommended



Rowing Company, Heidelberg



DOSB/Turnerschaft
Zweibrücken

PREVIEW: ESMO GUIDELINE FATIGUE

- The use of **modafinil and armodafinil** is not recommended for the control of CRF [II, D]
- The use of **L-Carnitine, coenzyme Q10, Astragalus, and Guarana** is currently not recommended for the control of CRF [II,D].

Panel has not reached consensus:

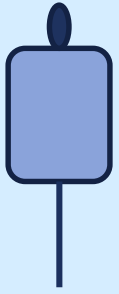
Methylphenidate, dexamethylphenidate, long-acting methylphenidate and dexamphetamine

Misteltoe extracts

Wisconsin ginseng

Acupuncture





Chemo-therapy

Radio-therapy



©K. Jordan

BENEFIT

Overall Survival

Progression-free Survival

RISK

Muscular Disorders	Thrombocytopenia Lymphedema	Constipation Sexual Dysfunction	Infection Anorexia	Fertility Lung toxicity	Malnutrition Osteoporosis	Anemia
Ototoxicity	Immune-related Toxicity	Paravasation	Pain	Fatigue	Nausea	
Allergic Reaction	Venous Thromboembolism	Rash	Alopecia	Vomiting		
Cardiotoxicity	Central nervous Toxicity	Neurotoxicity	Xerostomia	Psychological problems		
Skin toxicity	Diarrhoea	Mucositis	Hot flashes	Vascular disorders		
Tumorlysis	Renal Toxicity	Osseous Complications		Taste alteration		
Psychiatric disorders	Neutropenia					