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Abstract

Concurrent chemotherapy and radiotherapy (CCRT) followed by durvalumab immune therapy in appropriate patients is considered to be the standard of care in most fit stage III NSCLC patients. However, CCRT is a toxic treatment that affects all organ systems and may cause acute and permanent side-effects, of which some may be lethal. Supportive care is therefore of utmost importance in this clinical setting. A group of experts from the European Society for Therapeutic Radiology and Oncology (ESTRO) and the European Society of Medical Oncology (ESMO) identified the following items of importance for further improvement of supportive care: smoking cessation, nutrition before and during CCRT (including treatment and prevention of anorexia), physical exercise before and during CCRT, prevention and treatment of acute esophagitis and dysphagia, treatment of cough and dyspnea, treatment of skin reactions, treatment of fatigue, prophylaxis of nausea and emesis, prevention, diagnosis and treatment of cardiac disease and damage, and optimization of radiotherapy techniques and chemotherapy adjustments to reduce toxicity in the era of immune therapy.

The resulting recommendations were summarized in this manuscript and knowledge gaps identified, in which future investments are needed in order to improve supportive care and hence quality of life and survival for our stage III NSCLC patients.

Key-words:

supportive care, recommendations, guidelines, ESMO, ESTRO, lung cancer

Introduction

Stage III non-small cell lung cancer (NSCLC) is a very heterogeneous disease [1]. Concurrent chemotherapy and radiotherapy (CCRT) is considered to be the standard of care in most fit stage III NSCLC patients (1). CCRT is mostly defined as the administration of radiotherapy to the primary lung cancer and the involved lymph nodes, typically at a dose of 60 – 66 Gy given in 2 Gy once-daily fractions, five times per week, together with two cycles of a platinum-doublet chemotherapy. Recently, 12 months of adjuvant immunotherapy (durvalumab) has shown to improve the overall survival (OS) following CCRT [2].

However, CCRT is a toxic treatment that affects all organ systems and may cause acute and permanent side-effects, of which some may be lethal [1]. Supportive care is therefore of utmost importance in this clinical setting. This relates not only to the prevention and treatment of infections, the use of anti-emetics for chemotherapy and sometimes hematopoietic growth factors administration, but also to meticulous radiotherapy planning and delivery, for all of which excellent recommendations exist [3-5]. A group of experts from the European Society for Therapeutic Radiology and Oncology (ESTRO) and the European Society of Medical Oncology (ESMO) identified the following items of importance for further improvement of supportive care: smoking cessation, nutrition before and during CCRT (including treatment and prevention of anorexia), physical exercise before and during CCRT, prevention and treatment of acute esophagitis and dysphagia, treatment of cough and dyspnea, treatment of skin reactions, treatment of fatigue, prophylaxis of nausea and emesis, prevention, diagnosis and treatment of cardiac disease and damage, and optimization of radiotherapy techniques and chemotherapy adjustments to reduce toxicity in the era of immune therapy.

Smoking cessation

Persistent smoking after cancer diagnosis has been shown to have a significant impact on overall mortality, cancer-specific mortality, risk for second primary cancer, quality of life, efficacy of treatment and cancer treatment toxicity across all cancer sites and treatments. This applies also for lung cancer [6-8].

There is inconsistent data that smoking lowers the risk for developing radiation pneumonitis, which may be due to the different definitions of pneumonitis, the in-or exclusion of alternative diagnoses of dyspnea and the inclusion or not of baseline dyspnea in a multivariate model [3]. Continuing to smoke during radiotherapy or chemo-radiotherapy for lung cancer may lead to a decreased overall survival [8-11]. Patients who continued to smoke after treatment for early stage lung cancer (stages I-IIIA) had a higher risk of tumor recurrence, development of a second primary tumor or all-cause mortality compared with those who quitted smoking [12].

Smoking cessation, before or after radiotherapy for lung cancer, increases the performance status and HRQoL (health related quality of life) and may also lead to improved survival [13-14]. Smoking cessation was shown to be associated with a decreased risk for a second smoking-related primary cancer in small cell lung cancer patients who survived cancer-free for more than two years after initial successful therapy [15].

Whether completely switching tobacco cigarette smoking to vaping of an e-cigarette improves outcome of lung cancer patients treated with chemo-radiotherapy, has not been established [16].

Current smokers with stage III lung cancer considered for CCRT should be actively supported to quit smoking. This recommendation is very likely also applicable for patients receiving sequential chemotherapy and radiotherapy, radiotherapy alone, or any anticancer non-surgical or surgical treatment. Smoking on itself is not a contra-indication for receiving CCRT. Cancer diagnosis is a 'teachable' moment to assist the patient to quit smoking and immediate smoking cessation may significantly decrease the risk of complications and also improve overall survival [6,13]. No studies

have shown any harm from smoking cessation in cancer patients, or any signal for a clinical benefit of continued smoking [17,18].

Prevention and treatment of acute esophagitis and dysphagia

Acute esophagitis and dysphagia occur in most patients receiving concurrent chemotherapy and radiotherapy for stage III NSCLC, with an incidence of 20 % reversible CTCAE grade 3 dysphagia [19]. Acute radiation-induced esophagitis typically begins during the third week of CCRT and reach a peak approximately two weeks after the end of CCRT. Healing is mostly complete about 8 weeks after the end of CCRT.

Disorders of the esophageal motility may also lead to dysphagia [20]. Severe, long-lasting acute esophagitis may evolve to late damage such as strictures and perforation. Serious acute esophagitis may not only result in a decreased intake of food, but also of liquids, which may lead to dehydration. Adequate nutritional support and weight control is necessary, as discussed in the section on nutritional support below.

There is a good correlation between dysphagia and esophagitis in radiotherapy patients [21,22]. Patients with clinical grade 2 or 3 dysphagia also had endoscopic evidence of esophagitis [21,22]. 11% of patients without or with clinical grade 1 dysphagia had grade 3 esophagitis, scored by endoscopic criteria [22]. 16 % of patients had esophageal candidiasis; the relation with dysphagia or endoscopic grade was not reported.

An increased esophageal transit time (ETT) may also lead to dysphagia [23]. Radiotherapy increases the ETT in 80 % of patients, even at low doses [21,24]. There are no data available on the ETT at higher doses or with CCRT, but most likely the severity and incidence of increased ETT will be higher. It is unknown when and if the esophageal motility returns to normal after CCRT.

Amifostine, a radioprotective thiol, was evaluated in three randomized trials [25-27]. In one of the three trials (n=146) amifostine reduced the incidence of esophagitis in week 4 during radiotherapy [25]. However, the two other trials with 243 and 60 patients, respectively, could not show a beneficial effect [26,27].

Two small placebo-controlled randomized trials totaling 14 and 28 patients, respectively, investigated indomethacin or naproxen [28,29]. No effect on esophagitis was observed. Twenty-nine percent developed esophageal candidiasis, with no difference between the groups.

A placebo-controlled randomized trial (n=97) did not demonstrate a beneficial effect of sucralfate, a cytoprotective drug used to treat gastro-intestinal disorders on dysphagia [30].

In NRG/ RTOG 1012, 163 patients were randomized between prophylactic Manuka honey and standard supportive care during CCRT [31]. Standard supportive care consisted of viscous lidocaine, an antacid, and oxycodone as needed. There was no statistical difference in patient-reported pain on swallowing.

Because esophageal candidiasis frequently occurs, evaluation of patients with grade 2 or more esophagitis should include a physical examination for the mouth and oropharynx for candidiasis. Patients who have a delayed recovery of esophagitis, esophageal candidiasis should be suspected and anti-fungal therapy may be considered.

Nutrition before and during CCRT, including treatment and prevention of anorexia

In cancer patients undergoing curative or palliative cancer therapy, malnutrition and cachexia, including weight loss and metabolic dysregulations, are associated with an impaired prognosis and may therefore be targets for prevention and treatment [32,33]. In patients with lung cancer, malnutrition is a common co-morbidity [34]. Patients receiving CCRT for stage III lung cancer are at a high risk of worsening of this condition related to esophagitis and dysphagia resulting in inadequate nutritional intake [32,34]. This is further exacerbated by the cancer itself and treatment-induced catabolism, anorexia, nausea, abdominal discomfort, fatigue, pain, anxiety, depression and other psycho-social distress [32,35].

Because of the increased risk of malnutrition, nutritional risk should be assessed and all patients counselled before and during therapy [32,36-38]. Counselling by trained professionals has been shown to improve energy and protein intake, body weight and quality of life [32,36].

Nutritional assessment should be performed by a nutrition expert and includes calculating body mass index, estimating food intake, determining the presence and degree of weight loss, muscle mass, anorexia and other nutritional impact symptoms (e.g. nausea, dysphagia, diarrhea), decreased performance index and metabolic derangements as well as the presence of other stressors like pain, psychological and social distress [32,35].

Prevention of nutritional deficits should include early counselling on the potential stressors listed above [37,38], options to improve food intake and physical activity and on the need to seek professional help early in case of developing symptoms. To prevent or minimize the symptoms of esophagitis and dysphagia, it is crucial to instruct patients to avoid alcohol, bulky food, spicy, hot or very cold food, citrus fruits and products, such as lemons, oranges and orange juice. Prevention also includes optimal anti-emetic prophylaxis, effective pain treatment, early psycho-social care when

required, exercise training, control of potential constipation and protection of the gastrointestinal mucosa.

Independent of the route of delivery, nutritional intake should cover at least 30 kcal and 1.0-1.5 g protein per kg body weight as well as the recommended daily allowance (RDA) for all micronutrients [32,37,38]. If intake is expected to be inadequate, counselling should focus on the choice of foods, options to enrich foods with energy and proteins, optimal meal size and meal frequency. Pain induced by chewing or swallowing needs to be controlled effectively. Counselling should focus on soft and mild food avoiding irritating ingredients. Liquid or soft oral nutritional supplements should be offered in addition to, but not in replacement of normal foods. If oral intake is inadequate despite meticulous care, resulting in progressive weight loss of 5% from the initiation of CCRT, tube feeding should be initiated promptly. In patients receiving CCRT for stage III lung cancer, naso-gastric tube feeding is rarely required for prolonged periods of time. In very rare situations, such as in important anatomical deformations or intolerance for a naso-gastric tube, placement of a percutaneous endoscopic gastrostomy (PEG) should be considered. If enteral tube feeding is not tolerated, parenteral nutrition should be offered [32].

No pharmacologic agent has shown to improve anorexia or catabolism in this setting [32]. Data reporting effects of glutamine or long-chain N-3 fatty acids on appetite, body weight and lean body mass in patients with lung cancer are heterogeneous and based on trials characterized by a definitive risk of bias [32].

Physical exercise before and during CCRT

The health benefits of exercise have been recognized in cancer patients [39]. However, patients with lung cancer tend to have low levels of activity and a reduced tolerance to exercise. This can be explained by the presence of disabling symptoms such as fatigue and shortness of breath due to existing co-morbidities or to the cancer itself, which impact on the patients' ability to engage with exercise. Chronic obstructive pulmonary disease (COPD) is present in ~70% of men and ~50% of women with newly diagnosed primary lung cancer in Europe [40]. There is evidence of reduction in hospitalization and improvement in health-related quality of life in COPD patients taking part in pulmonary rehabilitation programs that include home-based exercise [41,42].

Although some studies have investigated physical exercise in lung cancer patients, there is paucity of data specifically in patients treated with chemo-radiotherapy. Most of the data available comes from the surgical setting [43]. Exercise training in patients with advanced lung cancer showed an improvement in disease-specific global HRQoL but no significant effects on dyspnea, fatigue, feelings of anxiety and depression, or lung function [44,45].

Only two studies were identified in the setting of radical treatment (surgery or radiotherapy, with or without chemotherapy) for lung cancer. In the first study, 28 patients were randomly allocated after to either standard follow-up or a 12-week rehabilitation training program [46]. The study showed that muscle mass and strength are decreased at presentation in most patients and decline after radical treatment. Furthermore, muscle mass and strength completely recovered after a 12 week structured rehabilitation program, whereas a further decline was observed in the control group. In the second study, 70 patients were randomized to either a resistance training program, whole body vibration or standard follow-up [47]. The primary endpoint was a change in 6-min walking distance (6MWD) after rehabilitation. The study showed that radical treatment significantly impaired patients' exercise capacity. Resistance training significantly improved and restored functional exercise capacity. In both studies compliance was an issue.

Treatment of cough and dyspnea

Cough and dyspnea during and after radiotherapy may be caused by either acute radiation bronchitis or pneumonitis (occurring during or 2-6 months after radiotherapy, respectively) or by pulmonary fibrosis (mostly 6 months or more after radiotherapy). Radiation-induced lung injury (RILI) is a complex process of subacute and chronic cellular and molecular mechanisms, involving damage to alveolar epithelial cells and vascular endothelial cells, activation of macrophages, fibroblast accumulation, proliferation and differentiation which can lead to radiation-induced pulmonary fibrosis, typically 6-12 months following completion of radiotherapy [48,49]. Most important RILI symptoms are a nonproductive cough, exercise-induced dyspnea, low-grade fever, and chest pain. However, some 45% of lung cancer patients, treated with radiotherapy, may develop cough and dyspnea not related to the radiotherapy, alternatively caused by pulmonary infections, COPD exacerbations, heart failure, cardiac arrhythmias, anemia, immunotherapy-induced lung tissue changes [49]. The recent introduction of immunotherapy in the combined treatment of locally-advanced NSCLC patients, was associated with an increase in pulmonary toxicities of any grade in the PACIFIC trial, but grade 3-4 toxicity was not significantly increased in the anti-PD-L1 immunotherapy durvalumab arm versus the control arm [2]. In all of the recent chemo-radiotherapy trials, the frequency of grade ≥3 acute pulmonary toxicities was well below 5 % [3,49-51].

Smoking cessation is associated with a decrease of cough and dyspnea and should be encouraged [52,53]. Special attention should be paid towards the dose and volume of lung irradiated in patients with interstitial lung disease. These patients should be more intensively counselled about their elevated radiation pneumonitis risk [54]. More intensive follow-up may be needed in this group of patients in order to detect pulmonary toxicity earlier [55].

Treatment of cough and dyspnea caused by radiation pneumonitis consists of symptomatic treatment (inhaled beta2-mimetics; oxygen supplementation) anti-inflammatory drugs (use of

corticosteroids, moderate to high-dose and tapered over several weeks) and treatment of comorbid diseases [49,54].

Treatment of skin reactions

Radiation effects in the skin mostly manifest within 2-3 weeks of radiation start, may increase for 1-2 weeks after radiotherapy has finished and gradually resolve over a period of 3-4 weeks after treatments have been completed [55].

Severe radiation-induced skin reactions are rare in patients receiving CCRT for lung cancer [2,49-51]. Moist desquamation is observed in fewer than 5% of patients with most patients experiencing no change to skin or faint erythema and dry desquamation.

The addition of anti-PD-L1 immunotherapy durvalumab after CCRT did not increase skin reactions [2].

When asymptomatic, radiation-induced skin reactions do not require treatment. Dry desquamation may be treated with a moisturizing cream [55,56]. There is no strong evidence supporting the use topical steroids and dexpanthenol-containing emollients [55-57]. Avoiding sun exposure and wearing loose-fitting clothing may be helpful. Moist desquamation is treated as a superficial burn, mostly using hydrogels.

Treatment of fatigue

Fatigue is described as a feeling of physical and mental tiredness and is the most common symptom experienced by patients during cancer treatment. It also influences the HRQoL after completion of therapy in lung cancer survivors [58]. For all supportive and palliative care interventions - as well as for fatigue - a screening and assessment should begin at diagnosis and be continued at regular intervals [59]. To diagnose fatigue early, a patient-reported 10-point Numeric Rating Scale (NRS) might therefore be suitable to grade the intensity of fatigue as mild [58-60], moderate [61-63] and severe [64-67]. Patients reporting moderate or severe fatigue should undergo a follow-up assessment to identify the causes or other medical conditions that need treatment (e.g. pain, anemia or active infection) [60].

So far, there is no drug that can be recommended for the therapy of cancer related fatigue (CRF). The use of psychostimulants like methylphenidate [61], dexmethylphenidate [62], long-acting methylphenidate [63], dexamphetamine [64], modafinil [65] and armodafinil [66] is not recommended since their therapeutic efficacy could not be convincingly and reproductively proven. Also, antidepressants [67] or the acetylcholinesterase-inhibitor donepezil [68] showed no therapeutic benefit in the treatment of CRF. The short term use of corticosteroids (in trials: dexamethasone: 4 mg twice a day for 14 days; methylprednisolone: 16 mg twice a day for 7 days) might be considered [69,70]. The use of dietary supplements such as L-carnitin [71] and coenzyme Q10 [72], have turned out to be ineffective in randomized controlled trials. The intake of Wisconsin ginseng has led to an improvement in fatigue in a randomized double-blind study with 364 patients of all cancers undergoing or having undergone treatment with curative intent [73]. Although ginseng seems to be safe, further studies have to confirm these findings before definite recommendations can be made.

Growing evidence suggests that physical exercise is appropriate, not only to improve CRF, but also to reduce other side effects of therapy and to control loss of muscle mass [74]. Moderate-intensity exercise like walking, running, swimming or cycling 2-3 times per week for 30-60 minutes if possible

should be offered to the patients [75]. Furthermore, psychosocial interventions such as psychotherapy or psycho-education, including counselling about CRF, are of great importance. These programs can be helpful to develop strategies with the patients to handle fatigue-promoting or energy-consuming activities [76].

Prophylaxis of nausea and vomiting

In patients with lung cancer, chemotherapy and/or radiotherapy-induced nausea and vomiting (CINV/RINV) can occur within the first 24 h of therapy (*acute*) and 24 h to 5 days after therapy (*delayed*) or as a conditioned response in subsequent cycles of the antineoplastic therapy (*anticipatory emesis*). In table 1 the major classes of antiemetic agents are shown. At equivalent doses and bio-availabilities, oral and intravenous routes have equivalent efficacy and safety. The emetogenic risk potential of the antineoplastic agent determines the likelihood of CINV. In combination therapies, the preventive antiemetic strategy is based on the drug with the highest emetogenicity level (high, moderate, low or minimal) (examples table 2), which in concurrent chemo-radiotherapy for stage III lung cancer is mostly cisplatin. Carboplatin is moderately emetogenic, whereas etoposide, paclitaxel and vinorelbine are low emetogenic. Thoracic radiotherapy has a low emetogenic risk, and durvalumab is of low emetogenic potential [2].

If optimal antiemetic prophylaxis has been given and CINV occurs, repeated dosing of the same agents is unlikely to be successful. Possible rescue anti-emetics are shown in table 3 [78].

Prevention, diagnosis and treatment of cardiac disease and damage

All parts of the heart can be affected by radiotherapy, some even at low doses [79]. It is likely that underlying heart disease may make the heart more susceptible for radiation injury.

Due to massive technical improvements of radiotherapy, moving from two-dimensional (2D) technology to 3D in the late 1990, to Intensity Modulated RadioTherapy (IMRT) in the first decade of this century to Intensity Modulated Proton Therapy (IMPT) at present, the radiation dose to the heart has been reduced substantially. These modern techniques should therefore be considered standard practice, particularly in patients with existing cardiac co-morbidities.

The heart and the lungs can be viewed as a functional entity. This explains the preclinical findings that reducing pulmonary damage by radiation also mitigates cardiac functional damage [80]. Lung damage may indeed cause pulmonary hypertension [81].

In a preclinical model, the angiotensin converting enzyme (ACE) inhibitor captopril significantly improved the breathing rate and decreased cardiopulmonary fibrosis and maintained the cardio-pulmonary structure, reduced radiation-induced pleural and pericardial effusion, resulting in an improved left ventricular end-diastolic pressure [82].

To the best of our knowledge, no prospective study in humans has addressed the prevention or treatment of radiation-induced cardiac injury. As already mentioned, ACE inhibition was effective in pre-clinical models [82]. Cardiac injury after radiotherapy is diagnosed and treated similar to non-irradiated subjects, although the pattern of coronary occlusion and the presence of fibrosis may be challenging.

Radiotherapy techniques and chemotherapy adjustments to prevent toxicity in the era of immune therapy

No clinically significant increase in the rate of side effects have been reported with the addition of immunotherapy compared to that of CCRT alone [2,83]. In the PACIFIC study, durvalumab immunotherapy was delivered after CCRT for up to 1 year. The rates of grade ≥3 events were similar in the durvalumab and placebo groups (grade ≥3 pneumonitis were 3.4% and 2.6%, respectively) [2]. In the phase 2 NICOLAS study, evaluating the safety of delivering nivolumab concurrently with CCRT and for up to 1 year after completion of treatment, no increased pneumonitis grade ≥3 was observed [83].

There is no evidence supporting modifications of routine radiotherapy techniques to prevent toxicity in the context of the use of immunotherapy. As advocated in the European Organization for Research and Treatment of Cancer (EORTC) recommendations for planning and delivery of radiotherapy for lung cancer, dose to thoracic organs at risk should be minimized, while maintaining target coverage [3]. This can be achieved through the use of advanced radiotherapy techniques [84,85]. Both the lung V20 (volume of lungs minus the Planning Target Volume (PTV) receiving 20 Gy) and the mean lung dose (volumes of lungs minus the Gross Tumor Volume (GTV), correlate with the risk of radiation pneumonitis [3]. The V20 or the mean lung dose should be kept below 35–37% and 20 Gy, respectively. The dose to the heart and the esophagus should be kept as low as possible but no clear safe threshold has be defined [3]. Furthermore it is unclear which regions of the heart are most sensitive to radiation injury and whether the delivery of immunotherapy increases the risk of heart toxicity [86].

Both carboplatin or cisplatin-based regimen are known to be safe in patients also treated with immunotherapy in the CCRT setting [2,83].

Discussion

Although concurrent chemotherapy and radiotherapy , followed by 12 months of adjuvant durvalumab, if appropriate, is considered to be the first choice treatment for the majority of patients with stage III non-small cell lung cancer [1,2], side effects are very common.

The recommendations are summarized in table 4. However, it is also clear that the level of evidence for most recommendations is low, pointing to important knowledge gaps needing more research. In general, there is a lack of understanding of the underlying pathophysiological and molecular mechanisms that contribute to the side effects caused by concurrent chemotherapy and radiotherapy with or without checkpoint inhibition. Cytotoxic chemotherapy and radiotherapy do more than just kill cells; they provoke a series of ill-defined processes affecting the whole body [49]. Promoting inflammation, modulating the innate and adaptive immune system as well as metabolic processes in the lungs, the heart, but also in other organs all lead to profound changes that contribute to side effects such as cachexia, anorexia fatigue, esophagitis, cough and dyspnea. The addition of immune checkpoint inhibitors further contributes to the complexity of these processes. At present, most preventive and interventional measures are symptomatic and do not tackle underlying mechanisms, simply because we do not understand them all in depth [49]. It is our view that future clinical studies should include translational parts that not only investigate effects of the treatment on the tumor, but also on different host systems. The identification of predictive and prognostic biomarkers will not only increase understanding of these underlying mechanisms but lead to the development of more targeted, less toxic therapies, improved quality of life and increased overall survival. It is envisaged that improved supportive care will lead to a higher success rate with less side effects of new treatment options and thus to higher cost-effectiveness. Pre-clinical models may be part of this research, but they cannot replace meticulous clinical investigation [87].

In the meantime, the implementation of these recommendations in clinical practice will benefit patients and all of them are achievable although some may require additional resources. Hopefully, stakeholders will be willing to invest in order to improve the outcome of our patients.

Key message

Supportive care is an integral part of CCRT. All aspects are important, including smoking cessation, prevention and treatment of acute esophagitis and nausea and vomiting, treatment of cough and dyspnea, skin reactions, fatigue, cardiac disease and damage, nutrition, physical exercise, radiotherapy techniques and chemotherapy adjustments in the era of immune therapy.

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Table 1 Major anti-emetics: class/drug, route, dose (emetogenicity of treatment)

Class/Drug	Route	Daily recommended dose [a]
5-HT_3-RA		
Dolasetron	p.o.	100 mg
Granisetron	p.o./i.v.	2 mg / 1 mg (0.01 mg/kg); transdermal via a patch over multiple days
Ondansetron	p.o./i.v.	24 mg (high)*, 16 mg (8 mg b.i.d. is recommended) (moderate)* 8 mg (0.15 mg/kg)
Tropisetron	p.o./i.v.	5 mg / 5 mg
Palonosetron	p.o./i.v.	0.50 mg / 0.25 mg (0.75 mg in Japan)
Steroids		
Dexamethasone	p.o./i.v.	12 mg (high with aprepitant)*; 20 mg without aprepitant: acute emesis 8 mg b.i.d. (high)*, 8 mg (moderate)*: delayed emesis
NK_1-RAs		
Aprepitant	p.o.	125 mg on Day 1; 80 mg on each of Days 2 and 3 160 mg on Day 1 (approved dose in Australia and Switzerland)
Fosaprepitant Rolapitant Netupitant	i.v. p.o. p.o.	150 mg one only on Day 1 180 mg once only on Day 1 300 mg netupitant/0.5 mg palonosetron once only on Day 1 one oral fixed combination
Atypical antipsychotic Olanzapine	p.o.	5-10 mg 2-3 days

[a] ()* reflects emetogenicity of therapy for a particular dose. b.i.d: twice-daily; p.o.: orally; i.v.: intravenously.

Table 2 Antiemetic prophylaxis recommendation for CINV according to the MASCC/ESMO and ASCO recommendation [4,77]

Level of emetogenicity	**Agent (examples)**	**Antiemetics Acute Nausea and Vomiting**	**Antiemetics Delayed Nausea and Vomiting**
High (> 90 %)	Cisplatin	5-HT_3 + DEX + NK_1 + (OLA)*	DEX +**APR + (OLA)*
Moderate (30-90 %)	Carboplatin	5-HT_3 + DEX + NK_1	None or ** APR
	Other than Carboplatin	5-HT_3 + DEX	No routine prophylaxis
Low (10-30 %)	Etoposide, Docetaxel, Durvalumab, Paclitaxel, Gemcitabine, Pemetrexed	5-HT_3 or DEX or DOP	No routine prophylaxis
Minimal (< 10 %)	Vinblastine Vincristine Vinorelbin	No routine prophylaxis	No routine prophylaxis

5-HT_3: Serotonin$_3$ receptor antagonist, DEX: Dexamethasone, NK_1: Neurokinin$_1$ receptor antagonist, DOP: Dopamine receptor antagonist, OLA: Olanzapine

*In patients treated with highly emetogenic chemotherapy olanzapine may be considered with a 5-HT_3-RA plus dexamethasone, plus an NK_1-RA (MASCC/ESMO guideline Update 2017). In the ASCO guidelines Olanzapine is recommended in this setting.

**If APR 125 mg for acute, otherwise no NK_1-RA is necessary on day 2 and 3.

Table 3 Rescue anti-emetics

Drug	Dose
Olanzapine	1 x 5 mg p.o.
Haloperidol	1-3 mg daily
Metoclopramide	3 x 10 mg p.o. (maximum daily dose 0.5 mg/kg body weight, not exceeding 30 mg in total)
Levomepromazine	3 x 1-5 mg p.o.
Alizapride	3 x 50 mg
Lorazepam	1 x 1-2 mg p.o.
Alprazolam	1 x 0.25-1.0 mg p.o.
Dimenhydrinate	3 x 50-100 mg p.o. or 1-2 x 150 mg rectal

p.o.: orally

Table 4: Summary of recommendations

(See table 5, supplementary file, for the definitions of the levels and grading)

Smoking cessation

Smoking cessation should actively be supported in all patients, also before the beginning of treatment as it may improve long-term survival, decrease side effects and risk of developing second primary cancers (Level III, Grade A).

Prevention and treatment of acute esophagitis and dysphagia

The administration of a proton pump inhibitor at a daily dose of 40 mg, from the beginning of radiotherapy up to three months after the end is recommended (Level V, Grade B).

Because esophageal candidiasis frequently occurs, patients with grade 2 or more esophagitis may be given appropriate anti-fungal drugs (Level V, Grade B).

Symptomatic care, such as the administration of local anesthetics (e.g. lidocaine), systemic analgesics including opioids, is essential (Level V, Grade A).

Nutrition before and during CCRT, including treatment and prevention of anorexia

All patients should be offered assessment of nutritional risk and counselling by a trained professional before the start, during and after concurrent chemo-radiotherapy (Level III, Grade A).

Independent of the route of delivery, nutritional intake should cover at least 30 kcal and 1.0-1.5 g protein per kg body weight as well as the recommended daily allowance (RDA) for all micronutrients (Level III, Grade A).

Enteral or parenteral feeding should be initiated promptly if oral intake is inadequate resulting in loss of 5% or more of body weight despite meticulous care and support (Level III, Grade A).

Physical exercise before and during CCRT

Resistance training improves and restores functional exercise capacity and should be offered to patients after concurrent chemo-radiotherapy (Level III, Grade B).

Treatment of cough and dyspnea

The cause of cough and dyspnea should always be determined, and treatment should be initiated according to the etiology (Level V, Grade A).

Smoking cessation is essential, in conjunction with symptomatic treatment such as inhaled beta2-mimetics and the judicious use of corticosteroids (Level IV, Grade A).

Treatment of skin reactions

No preventive measures have to be taken to avoid skin toxicity (Level V, Grade A).

Dry desquamation may be treated with a moisturizing cream (Level V, Grade A).

Moist desquamation is treated as superficial burns (Level V, Grade A).

Treatment of fatigue

Only the short term use of corticosteroids (dexamethasone: 4 mg twice a day for 14 days; methylprednisolone: 16 mg twice a day for 7 days) might be considered as pharmacological intervention to treat fatigue (Level II, Grade C).

Drugs other than corticosteroids, as well as dietary supplements have not convincingly shown a beneficial effect (Level of evidence II, Grade of recommendation B).

Moderate-intensity exercises such as walking, running, swimming or cycling 2-3 times per week for 30-60 minutes if possible should be offered to the patients (Level II, Grade B).

Prophylaxis of nausea and vomiting

As chemotherapy is the most emetogenic part of concurrent chemotherapy and radiotherapy treatment, anti-emetics should be given according to standard guidelines (Level I, Grade A).

Thoracic radiotherapy has a low emetogenic risk; prophylactic anti-emetics are therefore generally not recommended on the days that only radiotherapy is administered (Level I, Grade A).

Durvalumab has a low emetogenic potential (Level I, Grade A).

Prevention, diagnosis and treatment of cardiac disease and damage

Patients should avoid cardiovascular risk factors such as smoking, being overweight, eating an unhealthy diet and sedentary behavior (Level V, Grade A).

Radiotherapy techniques to decrease the dose to the heart as much as possible should be used (Level II, Grade A).

Cardiac disease should be diagnosed and treated as in non-irradiated patients (Level V, Grade A).

Radiotherapy techniques and chemotherapy adjustments to prevent toxicity in the era of immune therapy

Radiotherapy techniques, doses and fractionation as well as chemotherapy regimen should be delivered according to international guidelines and similar to what has been used in randomized clinical trials for concurrent chemotherapy and radiotherapy with or without immunotherapy (Level II, Grade A).

The radiation dose to organs at risk, including all parts of the heart, should be kept as low as possible (Level II, Grade A).

Table 5 (Supplementary file): ESMO Levels of evidence and Grades of Recommendation

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well- conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended