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Review Article

Hazards and risks in oncology: radiation oncology

Abstract

Adverse effects and hazards which have their origin from radiation using conventional techniques like 3-D conformal radiotherapy and total radiation doses are well known. However little is known about the sprectum of especially late toxicity after radiation using new technologies like intensity modulated radiotherapy (IMRT) combined with novel target volume and dose concepts. Since IMRT allows for selective protection of the large salivary glands this technique improves the intermediate term quality of life and is the standard of care despite many details need further prospective evaluation. Combining cytotoxic drugs and radiotherapy yield improved survival in well-defined high risk patients. However morbidity and mortality of these protocols are high and deserve special expertise and supportive therapy. EGF-receptor antibodies have gained well defined indications, albeit specific toxicities in combination with irradiation deserve prospective studies and special attention.

Keywords: intensitiy modulated radiotherapy, chemoradiation, adverse events, epidermal growth factor receptor, head and neck cancer

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Introduction

Radiation oncology is a mainstay in treating extracranial head and neck cancers. Its impact both as a single modality but also in combination with surgery and/or systemic therapy has been elucidated in numerous studies of different levels of evidence. A longstanding tradition over ten decades has led to an accumulated knowledge upon therapeutic and adverse effects of radiotherapy performed in conventional 2 dimensional and recently 3 dimensional radiation technique. Initially conventional xrays and telecobalt gamma rays were used and with the advent of electron accelerators in the second half of last century with photons and electrons. These developments led a to a large body of knowledge upon the volumes to be treated and their total and single radiation doses to be given to obtain high local control rates and keep acute and chronic adverse effects at a reasonable level. During last three decades unconventional fractionation schedules have been studied in prospective randomized studies in order to optimize tumor control but also to clinical course of acute and chronic adverse effects at normal tissue inevitably exposed to ionizing radiation dose causing treatment associated acute and late morbidity.

Shortly after computer tomography and magnetic resonance tomography revolutionized diagnostics of tumors both became the basis of individualized anatomy based radiation dose distribution planning. Another step forward was computerization including digital processing of linac accelerators used in medicine. New algorithms were established for individual dose calculation including Monte Carlo calculation which allowed much more sophisticated dose distribution in tumor and surrounding normal tissues and organs. This led to the clinical implementation of intensity modulated radiotherapy allowing different radiation doses within one target volume, e.g. higher doses to hypoxic subvolumes of a tumor (dose painting) [1].

Positron emission tomography has recently been integrated not only in the staging process [2] but also in the radiation therapy planning process. Different radiopharmaceuticals e.g. deoxyglucose, fmisonidazol were used to detect tumor subvolumes with different radiobiologically relevant chracteristics e.g. proliferation or tumor hypoxia. These characteristics may be exploited in order to optimize an individual dose distribution plan and thus increase local tumor control probability (biologic radiation planning) [3]. However correlation of tumor size in excised specimen and metabolic seems loose [4]. New dose distribution concepts and fractionation schedules including integrated boost harbour which has an at least in part unknown toxicity profile which may impact negatively on chronic morbidity particularly in long term surviving patients.

Another new therapeutic avenue became clinically important with increasing knowledge upon interaction between cytotoxic drugs and more recently target drugs and ionizing radiation on a cellular basis (e.g. radiosensitization of cells). Much experience with regard to tumor control and adverse effects has been accumulated with simultaneous and sequential chemoradiation after extensive clinical use in numerous studies. However this is not true at the same degree for drugs used in target therapy.

Intensity modulated radiotherapy (IMRT)

Radiation induced xerostomia is a major source for chronic morbidity after primary or postoperative radiother-

apy. Conventional 3D conformal radiotherapy does not allow sparing of the major salivary glands exept for few cases. Acute and chronic xerostomia causes a couple of adverse effects which impairs the quality of life in particular in long term survivors. Among others the most important are malnutrition and subsequent loss of weight, dental decay and chronic infection of the oral cavity. The technologically challenging intensity modulated radiotherapy allows for dedicated sparing of one or both parotid glands, which consequently results in lower probability of stimulated xerostomia provided radiation dose constraints, e.g. median organ dose of 26 Gy or less have been fulfilled [5], [6]. IMRT is associated with higher global quality of life compared to conventional 3D conformal radiotherapy [7], [8] which is particularly observed with increasing length of survival. The retrospective pattern of care data of the SEER showed equivalent tumor control and suvival figures at 5-years obtained in 1,600 patients treated with both methods [9]. For the individual not being treated in a radiation oncology department not experienced with IMRT eventually means an adverse factor with respect of his further quality of life [10].

However with increasing experience with IMRT it became clear that the departure from conventional radiation techniques may carry risks hitherto not known. With 3D conformal radiotherapy in primaries other than larynx and hypopharynx the lower neck nodes have been irradiated by a direct ventral portal and by shielding the spine the lower part of the paryngeal muscles have been shielded too. At the beginning of the IMRT era sparing of these muscles have not been recognized as important for preventing from dysphagia and aspiration and were initially not considered organs at risk. Not surprising that in a series of studies an increase of dysphagia after primary high dose chemoradiation using IMRT technique has been discribed [11]. Recent concepts focus on sparing of pharyngeal musculature, esophageal sphinctger and supraglottic larynx. Total doses of less than 60 Gy should reduce the risk of dysphagia and aspiration [12], [13].

Chemoradiation and radioimmunotherapy

Advantages and risks of chemoradiation

Conventionally used high total radiation doses (applied with 3D conformal technique), e.g. 70 Gy to advanced primaries and/or neck nodes result in local control rates of around 30%. Since these results cannot be improved by increased total radiation doses, cytotoxic drugs have been integrated in protocols giving chemotherapy simultaneously or sequentially to irradiation or more recently both.

When 5-fluorouracil, mitomycin C and cis-platinum are given simultaneously to radiotherapy, not only the cytotoxic effect contributes to tumor cell kill but an radiosensitizing effect of drugs is exploited.

Simultaneous chemoradiation using 5-fluorouracil and cis-platinum or mitomycin C or carboplatinum augmented loco-regional control rates in locally advanced cancer often considered inoperable due to local extension compared to radical radiotherapy alone. Since not only 3–5 years tumor control rates but also overall survival has been increased simultaneous chemoradiation has become the standard of care [14], [15], [16], [17], [18], [19].

Induction chemotherapy preceding definitive radiotherapy results in an increased overall treatment duration of typically 12 to 15 weeks (in which tumor surviving stem cells may proliferate) and higher cumulated drug doses. The two metaanalyses however showed only a smaller increase of tumor control rates compared to simultaneous chemoradiation [Budach W, Pignon]. Noteworthy recent protocols including docetaxel have not been considered. When triplets consisting of taxane containing induction chemotherapy followed by radical radiotherapy and simultaneous taxane containing chemotherapy are given, increased median progression and overall survival span are reported compared to 5-fluorouracil based induction chemotherapy at the expense of more frequent hematologic °3/°4 toxicity [20], [21], [22]. In these studies increase progression free survival was essentially gained by better loco-regional tumor control. Although total drug amount delivered increased the risk of distant metastases has not been reduced [20], [21] pointing to distant metastases being the achilles' heel of new concepts. In a randomized comparison of immediate chemoradiation compared to induction chemotherapy followed by chemoradiation the latter resulted in a marginal increase in progression free survival but no increase in overall survival at 3 years [20]. Acute toxicity of induction chemotherapy can jeopardize chemoradiation [23].

Postoperative radiotherapy is a standard of care in patients with loco-regionally advanced tumors with distinct pathohistological risk factors. In two randomized studies of the RTOG and EORTC patients with risk factors R1-status, extracapsular spread and more than 3 involved lymph nodes benefitted from the additional simultaneously applied chemotherapy [24], [25]. However a subgroup analysis of the RTOG study showed increased survival only in patients with R1-status and extracapsular spread of involved lymph nodes [26]. Since chemoradiation exposes patients with a treatment associated lethality of 1–4%, it is crucial to restrict chemotherapy to those who are likely to benefit.

An organ sparing strategy is persued particularly in patients who would need a total laryngectomy for cure of their laryngeal or hypopharyngeal cancer. Radiotherapy can contribute to perserve organ and function. Historical data showed a concordant responsiveness of cancers to chemo-and radiotherapy. Therefore in actual protocols a short induction chemotherapy select those cancers suitable for further chemoradiation and sort out those which need early salvage surgery. Also for smaller tumors simultaneous, sequential chemoradiation and radiotherapy alone was studied in a RTOG protocol. Like in other

primary tumor sites simultaneous chemoradiation was superior [27]. This protocol however carries a higher risk of late laryngeal toxicity compared to sequential therapy (15 vs. 10%).

Therapy associated morbidity of simultaneous chemoradiation

In loco-regionally advanced cancers simultaneous chemoradiation results in a 6–8% gain in 5-year survival compared to irradiation alone at the expense of increased acute morbidity. In these protocols the clinically leading toxicity is (often reversible) hematologic. When the treatment is intensified beside hematologic toxicity other not dominating adverse effects like nausea and emesis, alopecia, dysphagia, stomatitis, neuropathy and others also increase in frequency and serverity. However they are less likely assessed. This "underreporting" leads to an unjustified favourable estimation of intensified protocols [28]. Not only acute morbidity is augmented but also subacute adverse effects are reported to be more frequent 3 months after end of chemoradiation compared to radiation alone [29]. Beside acute morbidity late adverse effects, e.g. 5 years after end of chemoradiation gain increasing interest. However data are more scarce compared to those of acute morbidity [24], [30]. Among chronic symptoms aspiration and dysphagia, both vital risks, are increasingly investigated.

Among all cytotoxic drugs cis-platinum, carboplatin, 5-fluorouracil and taxanes are the drugs most used in modern protocols. When radiotherapy and cis-platinum are combined, acute adverse effects increase. Given in postoperative protocols °3+ (WHO) adverse effects increase from 34% to 77% compared to irradiation alone. Hence only 60% of all patients receive all 3 scheduled courses [25]. The toxicity profile change when cytotoxic drugs are administered concomitantly. Neuropathy and nephropathy are emerging risks which forces on intensified clinical monitoring but also intensified supportive care including optimized enteral feeding [31].

Cis-platinum is administered in anglo-saxonian protocols often on day 1 and 29 at a dosage of 100mg/kg body weight. In central europe the application of the same dose over 5 days (5 times 20 mg/kg body weight day 1–5, 29–33) has become standard in protocols. With the latter dosage the same tumor control rates are achieved with lower hematologic side effects [32].

In patients with preexisting diabetes mellitus more variation of their blood glucose profile have been observed when treated with cis-platinum for head and neck cancer. This may be due to an altered glucose metabolism. An intensive blood glucose monitoring is mandatory and existing medical antidiabetic therapy has to be adapted or initiated if no medication was applied before [33]. A cis-platinum associated hyperglycemic koma has been described [34].

The large salivary glands are highly radiosensitive. Due to their proximity to the target volume (tumor or tumorbed and safety margins) it is often impossible to spare them from high radiation dose applied to the target volume. If one parotid gland is exposed to a median cumulated dose of 26 Gy or more irreversible subacute and chronic xerostomia must be anticipated [6]. Even lower median doses have been advocated [5]. If cis-platinum is given simultaneously to irradiation the tolerance of salivary glands and residual salivation further decreases [35]. If cis-platinum is used in a simultaneous chemoradiation protocol, a radiation technique should be applied which allows an optimal sparing of at least one parotid gland. In these cases the target median dose should probably be less than 26 Gy in order to reduce the risk of permanent xerostomia. This is best accomplished by sophisticated intensity modulated radiotherapy which should be regarded as a standard of care in chemoradiation protocols. Further improvement of parotid gland sparing is achieved by radiotherapy with protons [36], which however is not available for a larger population. Moreover chemoradiation protocols are associated with a treatment related mortality of 1–4% [14], [19], [26], [27], [37]. Particularly in polymorbid patients these hazards need to be counterbalanced critically against the possible gain in survival achieved by addtional chemotherapy.

New concepts by antibodies and tyrosinkinase inhibitors

Considerable improvements have been achieved by radical and postoperative chemoradiation protocols. Despite intensification of treatment no further gain can be expected due to concomitant morbidity of most patients, which limits their tolerance and compliance. A particular issue are distant metastases, which are experienced more often as loco-regional control increases. As a consequence new drugs with more specific tumoricidal acitivity and less hematological and mucosal toxicity are investigated. Among the vast body of molecular strategies up to now only a few gained clinical significance or are studied in phase III trials: 1. monoclonal antibodies against the extracellular domain of the epidermal growth factor receptor (EGFR inhibitors), 2. the inhibition of intra-and extracellular domains with tyrosinkinase inhibitors with low molecular weight ("small molecules") (EGFR tyrosinkinase inhibitors) and 3. antiangiogenetic drugs against vascular endothelial growth factor (VGFR inhibitors) blocking the neoangiogenesis in tumors [38]. Currently in Europe only Cetuximab for EGFR inhibition has been approved in combination with radiotherapy of squamous cell head and neck cancers.

Cetuximab

More than 90% of all squamous cell carcinoma of the head and neck show an overexpression of the epidermal growth factor receptor, which is associated with lower survival [39]. Recent data show versatile acitivies of cetuximab at different cellular levels and clinical response does not closely correlate with the degree of cellular

overexpression of EGFR. The exact mode of action of cetuximab remains unclear [40]. Despite that cetuximab serves as an alternative to cis-platinum in clinical chemoradiation protocols for head and neck cancers. In the TREMPLIN protocol [41], a larynx preservation protocol, cis-platinum was randomized against cetuximab. Equivalent 2-year survival data without laryngectomy were reported (cis-platinum: 79%, cetuximab: 71%, n.s.). However cetuximab was associated with less protocol violation and less late morbidity.

Low acute toxicity is a charactistic of treatment with cetuximab. However the toxicity profile is different for that of cis-platinum. One typical side effect is the higher risk of radiation dermatitis °3–4 including skin necrosis, which is confined to the irradiated skin an differs from akneiform rash. Various studies observed radiation dermatitis up to 23% of patients [42], [43], [44]. For management of cetuximab associated radiation dermatitis recently multidisciplinary guidelines have been published [45], [46]. When antibodies against EGFR cetuximab or panitumumab are infused acute bronchospasm is occasionally observed and therefore monitoring is mandatory. Case reports of bronchiolitis and lung fibrosis are published [47]. Cetuximab may rarely cause hypocalemia and hypomagnesemia. When misdiagnosed the latter may proceed and cause convulsions and arrhythmia [48].

Cardiac toxicity of new drugs

A large hospital based survey admission diagnosis and prevalent comorbidity was analysed. Patients admitted with head and neck cancer had a higher incidence of cardivascular (41% vs. 27%) and obstructive lung (12% vs. 5%) disease compared to patients admitted due to a non-cancer diagnosis. During a 12 months follow-up patients treated with chemotherapy for their cancer experienced 1.7 fold chronic anemia and 2.6 fold a second cancer compared to the non-cancer patients [49]. For cetuximab no cardiac or hematopoetic adverse effects are documented. Therefore cetuximab may be the preferred drug for in comorbid head and neck cancer patients [50].

Hypothyroidism

Due to proximity of the thyroid gland and the target volume of radiotherapy of most tumors a large part of the gland inevitably will be exposed to high radiation doses. 6 months after exposure of the gland thyroid stimulation hormone will rise [51]. The incidence of a subclinical or clinical hypothyroidism will increase over years and has been observed even 20 years after radiotherapy. However with increasing time span, other etiologic factors may contribute [52]. Hemithyroidectomy and radiotherapy were predictive for hypothyroidism an a multivariate analysis [53]. Typically 10 years after radiotherapy a subclinical or clinical hypothyroidism is diagnosed in 20–25% in all irradiated head and neck cancer patients. Advanced radiation techniques like the IMRT are able to spare at least parts of the thyroid gland. However long term experience upon the incidence of hypothyroidism after IMRT is lacking. Irrespective of radiation technique and total dose used all patients need a yearly follow-up for their functional status. Radiogenic thyroid diseases are treated like spontaneously ones.

Notes

Competing interests

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