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Title:

Definitive concurrent hypo fractionated radiotherapy with weekly cisplatin in locally advanced SCCHN in COVID-19 era

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Running title:

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Definitive concurent hypofractionated radiotherapy with weekly cisplatin in locally advanced SCCHN

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Introduction

Head and neck cancer is considered the 6th most common cancer all over the world, with 890,000 new cases and 450,000 deaths in 2018 (1). The histologic type in more than 90% of head and neck cancer is squamous cell carcinoma (SCC) (2). The incidence of SCC in head and neck (SCCHN) continues to rise and is expected to increase by 30% in 2030, which means about 1.08 million new cases annually (3). Hospital-based studies in Egypt showed that SCCHN represents about 20% of all malignancies. The overall incidence of SCCHN in Egypt from 1999 to 2006 was approximately twice among males (476,000) than in females (273,000) (4). Males are affected significantly more than females, with a ratio ranging from 2:1 to 4:1 (5).

Tobacco and alcohol consumption are the high-risk factors of SCCHN (6). Human papilloma virus (HPV), especially subtypes 16 and 18 are implicated risk factors in oropharyngeal cancer (7). Some studies found an association between HPV and P53 gene mutation, as HPV expresses two viral proteins (E6 and E7 proteins) that inactivates P53 and pRB genes, causing genomic instability and malignant transformation (8). SCCHN arises from the mucosal epithelium of the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx. HPV associated SCCHN arises primarily from the palatine and lingual tonsils of the oropharynx, whereas tobacco associated SCCHN arises primarily in the oral cavity, hypopharynx, and larynx.

Squamous cell carcinoma of head and neck (HNSCC) is being increasingly treated by multimodality approaches combining surgery, radiotherapy, and chemotherapy. Randomized controlled trials have demonstrated major improvements in loco-regional tumor control from altered fractionation radiotherapy with chemotherapy as compared with conventional fractionation (9)

Altered fractionation schedules reduces tumor repopulation effect and seek to improve the therapeutic ratio between tumor cell killing and normal tissue damage.

hypo-RT utilizes a small number of fractions with a larger dose per fraction (> 2Gy per fraction), shortening overall treatment time compared to a CFRT (9). Although a shorter treatment time can be obtained by applying a higher dose per fraction, it might also result in an increase in the incidence of late complications

In a meta-analysis of 50 trials including a total of 9615 patients, the addition of synchronous chemotherapy to radiotherapy for locally advanced SCCHN resulted in an overall survival benefit of 6.5% at five years (10). However, this is associated with late toxicity and questionable improvement in the therapeutic ratio

The objective of this study was to investigate hypofractionated IMRT CRT with 62.5 Gy in 25 daily fractions over five weeks (2.5 Gy per fractions biologically equivalent dose to the tumor, 70.9Gy 10 and late reacting tissues, 114.6 Gy 3) [20] with synchronous weekly cisplatin 40mg/m2 in patients with high-risk stage II (T2N0, excluding glottic laryngeal) disease, stage III (T1-3 N1 or T3N0). And stage IV (T1-4N2 orN3)

Aim of work

The primary endpoint will be acute toxicity. Secondary endpoints included: late toxicity and quality of life; loco-regional control, disease free survival and overall survival.

Patient and method

This will be non-randomized clinical trial study of dose intensified hypofractionated 3D conformal or IMRT with synchronous weekly cisplatin 40 mg/m2 in the period from 2018 to 2021 in South Egypt Cancer Institute, Assiut, Egypt. in patients with AJCC high risk stage II (T2N0, excluding glottic laryngeal) disease, stage III (T1-3N1 or T3N0)and stage IV (T1-4N2 or N3) oropharyngeal, laryngeal or hypopharyngeal squamous cell carcinoma. A planned 62 patients would be recruited and treated with neoadjuvant chemotherapy TPF followed by hypo fractionated radiotherapy dose 62.5 Gy in 25 daily fractions over five weeks with synchronous weekly cisplatin 40mg/m2

Eligibility criteria

Patients will be enrolled in this prospective study have to fulfill the following criteria:

Have histologically or cytologically proven oropharyngeal, laryngeal or hypopharyngeal squamous cell carcinoma; with AJCC high risk stage II (T2N0, excluding glottic laryngeal) disease, stage III (T1-3N1 or T3N0) and stage IV (T1-4N2 or N3) locally advanced non metastatic stage II/IV SCCHN according to AJCC stage classification 2018(8th edition

Age>18 years and <75years

No previous treatment (neither chemotherapy nor radiotherapy(

Eastern Cooperative Oncology Group (ECOG) performance status of <2

Adequate organ function

Provide informed oral or written consent

Exclusion criteria:

prior surgical curative resection for primary tumor

patients with metastatic disease;

prior radiotherapy within the treatment field;

any relative contraindication to radiotherapy;

prior administration of EGFR monoclonal antibodies, signal transduction inhibitors or targeted therapies.

Active severe infection

Active concomitant malignancy

Pregnant and or lactating women

Pre-existing motor or sensory neurotoxicity >Common Terminology Criteria of Adverse Events (CTCEA) grade 2

Percutaneous endoscopic gastrotomy tube will be placed in case of compromised nutritional status (significant weight loss due to dysphagia at time of presentation.

Evaluation and follow up:

Pretreatment evaluation must include the following:

Full medical history and physical examination

Assessment of performance status

All patients had dental evaluation at baseline

Complete blood cell count with differential

Liver function tests, kidney function tests and 24 h urine creatinine clearance

Baseline pretreatment assessment of tumor will be required within 4weeks before start of treatment as measured by computed tomography or magnetic resonance and direct endoscopy

During the treatment period, the patients will undergo weekly physical examination and toxicity assessment

CBC and serum creatinine will be performed weekly, while 24h urine creatinine clearance have to be performed every 3 weeks

Assessment of tumor response by clinical examination and head and neck MRI or CT will be performed 6-8 weeks after completion of treatment

Endoscopy will be done at 8-12 weeks after the end of concurrent chemo radiation for pathological conformation of response

Patients have to be followed up by clinical examination every 2months during the first year, every 3 months for the subsequent 2 years and every 6months thereafter

Tumor response will be assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Toxicity from treatment will be graded according to (CTCEA) and Radiation Therapy Oncology Group (RTOG) criteria. Clinically significant toxicity will be defined as any grade 3 or 4 toxicity probably or definitely attributable to therapy

Radiotherapy and chemotherapy protocol:

All patients will receive neoadjuvant chemotherapy TPF given in 21 day cycle for 3 cycles in the form of Docetaxel 75mg/m2 IV on day 1 , cisplatin 100 mg/m2 IV on day 1, 5-FU 1000 mg/m2 by continuous IV infusion over 24 hours on day 1 through day 4 then hypo fractionated radiotherapy

All patients will undergo simulation, and treatment will be delivered through the megavoltage beam with linear accelerator with 6M using 3D-CRT or IMRT with head immobilization using thermoplastic head and neck mask. contrast enhanced CT images for treatment planning at 2-5mm intervals from vertex to below the carina. the clinical target volume (CTV) and organs at risk (OAR) will be outlined on the axial images. Delineation of target volume will be aided with a radiologist in difficult cases. A 5-10mm expansion margin will be applied to the (CTV) to obtain the planning target volume (PTV)

The gross tumor volume (GTV) will be defined as the primary tumor and involved lymph nodes, determined by clinical, endoscopic and imaging investigations. Involved lymph nodes will be defined as those > 10 mm in short axis diameter or presence of a necrotic center. The clinical target volume (CTV) will be the GTV and areas deemed at risk of microscopic disease. Three CTVs were delineated: CTV1, the GTV with an isotropic expansion of 10 mm (edited for natural barriers to disease spread including bone, air, fascia); CTV2, the remainder of the involved sub-site and nodal levels and uninvolved first echelon nodal levels; and CTV3, nodal levels deemed at lower risk of microscopic disease spread. Three planning target volumes (PTV1, PTV2, PTV3) will be defined by an isotropic expansion of 3 mm from CTV1, CTV2 and CTV3, respectively. Radiation doses to PTV1, PTV2 and PTV3 will be 62.5 Gy, 55 Gy and 50 Gy over five weeks, respectively, prescribed to the mean of the PTV. The planning targets included that minimum and maximum dose to the PTV will be within 95– 105% of the prescription dose and less than 5% of the volume outside the PTV

The concurrent chemotherapy will be weekly cisplatin 40mg/m2 with proper premedication and good hydration

Statistics:

All statistical calculations were done using SPSS (statistical package for the social science; SPSS Inc., Chicago, IL, USA) version 22. Data were statistically described in terms of mean ± standard deviation (±SD), or median and range when not normally distributed, frequencies (number of cases) and relative frequencies (percentages) when appropriate. For comparing categorical data Exact test was used instead of Chi square ($\chi 2$) as the expected frequency was less than 5. OS, PFS and DFS were estimated using the Kaplan-Meier method. P-value is always 2 tailed set significant at 0.05 level.

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