International Journal Dental and Medical Sciences Research
Volume 4, Issue 6, Nov-Dec 2022 pp 712-718 www.ijdmsrjournal.com ISSN: 2582-6018

A study of TPF v/s TP as induction chemotherapy in Locally Advanced head and neck cancers

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Submitted: 10-12-2022 Accepted: 20-12-2022

ABSTRACT

Aims And Objectives: A study of TPF v/s TP as induction chemotherapy in Locally Advanced head and neck cancers was done to observe and evaluate the patients for operability or downstaging (depending on the subsite) after induction chemotherapy; and to compare the response rate to chemotherapyandthe related toxicities observed in both arms of the study.

Methodology: All patients with Stage III, Stage IVA and IVB of inoperable advanced Head and neck cancers undergoing Induction Chemotherapy (ICT) with TPF (Paclitaxel, Cisplatin and 5-Fluorouracil) and TP (Paclitaxel and Cisplatin) were enrolled in the study from November2020 till August 2022 at the Department of Radiation Oncology, RMC, Pravara Institute of Medical Sciences, Loni. Patients were included after IEC approval. Patients were assigned in two arms and received 3 cycles of 3 weekly chemotherapy in each arm, after which they were evaluated for operability or downstaging depending on the subsite. During treatment, patients were assessed for acute treatment toxicities according to CTCAE 5.0. Response assessment was done according to the RECIST 1.1 criteria.

Results: A total of 22 patients were enrolled in the study, 10 in the TP arm and 12 in the TPF arm. All patients had tobacco addiction. 12 patients had synergistic tobacco and alcohol addiction. One, 14 and 7 were stage III, IVA and IVB respectively. The compliance Rate in our study was 68.18%. 70% versus 66% completed treatment in the TP and TPF arm respectively. Overall, in our study, patients had 4.5% Complete Response (CR), 45.45% Partial Response (PR), 4.5% Static Disease (SD) and 13.5% Progressive Disease (PD).Patients with Carcinoma Oral Cavity and Carcinoma Maxillary Sinus were assessed for surgical eligibility. 42.17% (7 out of 17) patients were eligible for surgery, out of which 5 underwent surgery. 2 opted to undergo definitive CTRT instead.20% in the TP arm had significant toxicities as compared to 83.33% in the TPF arm. Grade 3 and grade 4 toxicities were compared in both arms. In our study, 10% had anaemia in TP arm. 8.33% patients in TPF arm had Thrombocytopenia, Diarrhoea, Hyperkalaemia and Acute Kidney Injury.Response rate in both arms was 50%. Toxicities observed in the TP arm were negligible compared to TPF arm.

Conclusion: TPF is an established ICT regimen with favourable results but associated with a severe toxicity profile in Indian population. A weekly TPF regimen or TP can be used in patients with a low performance score, poor built, old age and associated comorbidities.

Key Words: Advanced head and neck cancers, Induction Chemotherapy, TPF, TP

I. INTRODUCTION

According to data compiled by WHO, 71% deaths worldwide were caused as a result of non-Communicable diseases in 2016. Non-communicable diseases are estimated to cause around 63% of total morbidity. In the report from National Cancer Registry 2020, Cancer was responsible for around 9% of the deaths out of the 63% of the Non communicable disease burden. (1) Decrease in infectious disease has led to increased

longevity and increased quality of life in the Indian population.(2)Head and neck cancers are malignant tumours comprising of the Oral cavity, Lip, Larynx, Pharynx, Paranasal sinuses and salivary glands or the upper aerodigestive tract. Approximately 600000 patients are affected with Head and Neck cancers worldwide. Out of these, around 60% present with locally advanced disease which is non metastatic.57.5% of the total head and neck cancers occur in Asia. Head and Neck Cancers make up 30% of the total cancer burden in India, out of which 60-80% present with locally advanced disease as opposed to 40% in developed countries. (1)Globocan 2020 report states that cancers of the lip and oral cavity were the second most common cancers by incidence, mortality and 5-year prevalence in India. Overall, Head and neck cancers are the most common cancers in the Indian population. (After adding incidence for all sites) (4)The most common cause of morbidity in head and neck cancers is due to uncontrolled loco-regional disease rather than due to distant failure. The predominant pattern of recurrence is also loco-regional. (3) According to the pooled data of hospital-based cancer registries of 2020, 66.6% of head and neck cancer patients were staged as Locally advanced, 25.2% as localized, 4.8 and 3.4% with unknown extent. (1)

The major causative agents attributable in the Indian population are smokeless tobacco, betel nut chewing, Pan Masala (that includes betel quid, areca nuts and slaked lime) and Gutkha as compared to smoking and alcohol worldwide. (6)

Delayed diagnosis is most reported in the subsites of oropharynx, hypopharynx and Oral cavity. Indian population often requires an aggressive treatment and optimal use of chemoradiation in comparison to the Western World because our patient profiles are different genetically and etiologically. As a result, they show more unfavourable outcomes. Factors include the age of the patient, nutritional and performance status, associated comorbidities, active smoking status and a differing genetic makeup. (5)

The use of induction chemotherapy for locoregionally advanced head and neck cancers continues to be an attractive treatment option even though many trials have shown little or no effect in the overall survival with ICT. (6) This was in the pre-taxane era. The MACH-NC trials meta-analysis of 31 trials did not show any significant survival benefit.(7) The TAX 323 and TAX 324 trials brought an advent of use of Taxanes in chemotherapy. The TPF regimen showed an improved survival benefit as opposed to cisplatin, 5-FU regimen and included various Head and Neck subsites. (8,9)

Administration of TPF is cumbersome. It is more challenging to deliver the TPF regimen in developing countries due to logistical factors, socio-economic and patient related factors. Logistical issues include bed availability for chemotherapy and administration of continuous iv infusion of 5-FU over 5 days. Affordability of chemotherapy is also an issue as TPF requires a robust support with GCSF and many patients belong to the lower income group. Many advanced Head and neck cancers present with severe malnutrition and uncontrolled comorbidities, which makes tolerance of this chemotherapy improbable. A common chemotherapy regimen practiced in Indian setting is Paclitaxel and Cisplatin regimen, which covers all the issues that arise with the administration of TPF. (10)

TPF is an effective regimen, but often not tolerated by patients. Thus, proposing an alternate regimen with Paclitaxel and Cisplatin could be tolerated better. This forms the basis of our study as many patients in advanced stages present at our centre and ICT as a modality can be effectively used with an optimum chemotherapy regimen.

II. METHODS

This study was undertaken in the department of Radiation oncology, Pravara Institute of Medical Sciences. After obtaining clearance from ethical committee all patients fulfilling inclusion and exclusion criteria were enrolled in the study. The inclusion criteria included advanced HNSCC patients deemed inoperable and are Stage III and Stage IVA and IVB,who were above 25 years of age and below 70 years of age and those who provided consent for participation in the study. Exclusion criteria included Patients that were already operated for Head and Neck cancer, Patients with history of second malignancy, in early stages (1 and 2), operable HNSCC and those who have already received a certain modality of treatment for HNSCC. It also excluded patients not fit for chemotherapy according to the Karnofsky scale. (KPS less than 50) and patients with carcinoma nasopharynx and carcinoma salivary gland.Patients were then evaluated by detailed history, general & systemic examination followed by haematological and relevant radiological investigations. TNM staging was done before assigning patients into an arm randomly.Patients underwent chemotherapy according to the schedule with TP Arm receiving Inj.Paclitaxel (175mg/m2)and Inj. Cisplatin (75mg/m^2) on Day 1 (D1). The TPF arm received Inj. Paclitaxel

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(175mg/m2) on (D1) followed by Inj. Cisplatin (100mg/m^2) D2 and Inj 5-FU 500mg/m^2/day continuous IV infusion for 5 days from D2-D6 with 5 days GCSF support 300 µg/day SC.

During treatment, patients were assessed for acute treatment toxicities according to the CTCAE 5.0 version.After completion of treatment, patients of carcinoma oral cavity and PNS were assessed for operability; and those of other subsites were assessed for downstaging by recording tumour response according to the RECIST criteria 1.1.

III. RESULTS

A Total of 22 patients were enrolled in the study, out of which 21 were males and 1 was female. 10 patients were enrolled in the in the TP armas compared to 12 patientsin the TPF arm. TP and TPF arm made up 45% and 55% of the sample size, respectively.The median age in this study was 49.5 years. Head and neck cancers have a male predominance. This was observed in our study. 95.45% (11/22) patients in this study were males and only one was female (in the TP group). All patients (22/22) had addiction history with tobacco use in this study. Thus, the inclusion criteria included stage III, Stage IV A and Stage IVB patients. Out of 22 patients, 1 patient (4.54%) was Stage III, 14 patients (63.63%) were of Stage IVA and 7 patients (31.81%) were of Stage IVB.

70% versus 66% completed treatment in the TP and TPF arm respectively. Overall, in our study, patients had 4.5% Complete Response (CR), 45.45% Partial Response (PR), 4.5% Static Disease (SD) and 13.5% Progressive Disease (PD). Patients with Carcinoma Oral Cavity and Carcinoma Maxillary Sinus were assessed for surgical eligibility.42.17% (7 out of 17) patients were eligible for surgery, out of which 5 underwent surgery. 2 opted to undergo definitive CTRT instead.The response rate (RR) calculated for our study was 50% for both TP and TPF arm. Thus, in our study TP and TPF showed similar efficacy. The toxicity profile when comparing two arms was drastically different in both arms.The results of this study cannot be considered statistically significant as because of the time constraints of the study. The sample size was also inadequate as it could not be reached due to COVID 19 pandemic, which was present during majority of the duration of the study.

Table no. 1 : General parameters of patients enrolled in the study

Parameters	TP (10)	TPF (12)	Total (22)
Median Age	53 YEARS	47 YEARS	49.5 YEARS
Proportion of Males (in percentage)	90% (9)	100% (12)	95.45% (21)
Site: Oral Cavity	60% (6)	91.6% (11)	77.77% (17)
Site: Oropharynx	20% (2)	8.34% (1)	13.6% (3)
Site: Paranasal Sinus	20% (2)	0	9.09% (2)
Stage III	0	8.34%(1)	4.54%
Stage IV A	70%(7)	58.33%(7)	63.63%
Stage IV B	30%(3)	33.33%(4)	31.81%
WDSCC	30%(3)	25%(3)	27.27%(6)
MDSCC	40%(4)	35%(3)	31.81%(7)

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PDSCC	10%(1)	16.66%(2)	13.6%(3)
INVASIVE SCC	10%(1)	33.33%(4)	22.72%(5)
SCC NOT SPECIFIED	10%(1)	0	9.09%(2)

WDSCC: Well differentiated Squamous cell carcinoma; MDSCC: Moderately differentiated Squamous cell carcinoma PDSCC: Poorly differentiated squamous cell carcinoma; SCC: squamous cell carcinoma

Table 2: Addiction patterns

	TP	TPF	TOTAL
Alcohol	5	11	16
Chewed tobacco	6	10	16
Guthka	4	2	6
Mishri	3	3	6
Beedi	2	2	4
Cigarette	0	1	1

Graph 1: Addiction pattern in each arm

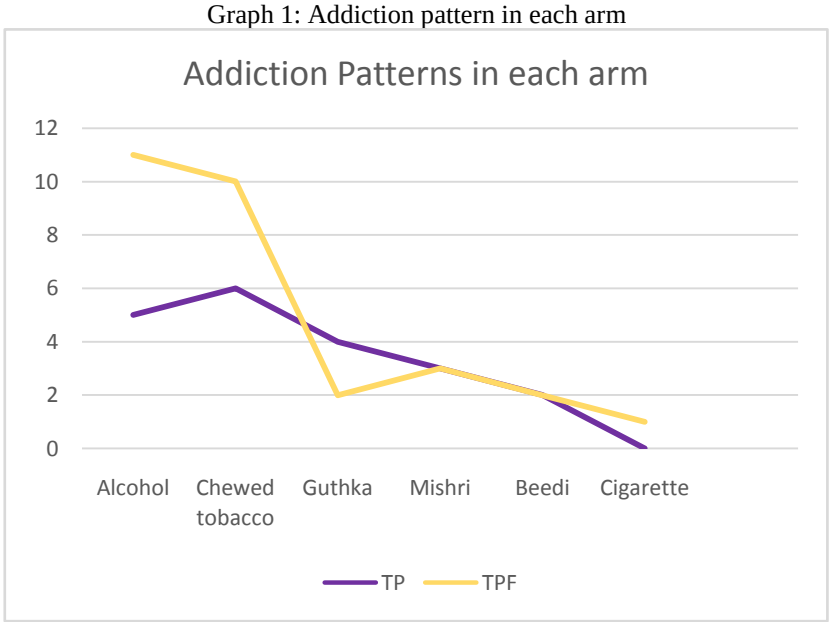

Table 3: Treatment Response

Parameters	TP	TPF	TOTAL
Compliance in percentage	70%	66%	68.18%
CR	-	8.33%	4.5%
PR	50%	41.66%	45.45%
SD	10%	-	4.5%
PD	10%	16.66%	13.6%
Response Rate	50%	50%	50%

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Table no. 4: Types of toxicities in both arms

	TP	TPF	TOTAL
Haematological	1	2	3
Anorexia	1	5	6
Nausea	0	7	7
Diarrhoea	0	1	1
Allergic reaction	0	1	1
Electrolyte imbalance	0	1	1
Deranged renal function	0	1	1
Not significant	8	2	10

Table No 5: Grade 3 and 4 reactions

	TP	TPF	TOTAL
Anaemia	10%	-	10%
Thrombocytopenia	-	8.33%	8.33%
Diarrhea	-	8.33%	8.33%
Hypercalcemia	-	8.33%	8.33%

IV. DISCUSSION.

Rural tertiary centres, like ours receive a lot of patients for diagnosis as well treatment. Many Head and neck cancer patients that present in the Oncology OPD are locally advanced and are often not eligible for upfront surgery. The patients may often present with a with massive nodal mass, fungating ulceroproliferative lesion, orocutaneous fistula, pus draining sinus, brachial plexopathy, stridor that can require urgent tracheostomy, severe trismus etc. They rarely present with distant metastases, in accordance with the natural history of disease. In a selected population, Organ preservation strategies by ICT or use of ICT for downstaging and operability can be considered.

According to NCCN guidelines, ICT for Locally Advanced Head and Neck Cancers falls under Category 3 evidence. (11) Current ESMO guidelines also classify ICT as a controversial therapy in unresectable HNCs (6). As of now, the role of ICT is confined to organ preservation in advanced laryngeal, oropharyngeal and hypopharyngeal cancers. A clear consensus has been reached for using ICT as a larynx preservation strategy in which definitive clinical trials have taken place. (8,12)The role of ICT in oral cavity cancers has been explored for downstaging unresectable tumours and making them resectable. Currently, no significant trials conferring increased OS or DFS after ICT regimen have been seen. (7)

Resectability is a relative term, but it usually denotes an R0 resection with negative clinical margins. If there are doubts in achieving such resection margins, ICT can be considered for downstaging.

In our study, Patients with Carcinoma Oral Cavity and Carcinoma Maxillary Sinus were assessed for surgical eligibility. Both patients (out of 2) of Maxillary sinus were eligible for surgery and both were from the TP arm. 42.17% (7 out of 17) patients were eligible for surgery, out of which 5 underwent surgery. 2 opted to undergo definitive CTRT instead. 27.27% were not eligible as a result of static disease or disease progression and 23.52% could not be assessed as the patients defaulted or passed away.

The response rate (RR) calculated for our study was 50% for both TP and TPF arm. Thus, in our study TP and TPF showed similar efficacy. However, in the study by Noronha et al., (10) the RR for TP was 22% as compared to 50% in TPF regimen. Patil et al. (13)had RR of 37.89% for 2 drug regimen and 68% for 3 drug regimen. Joshi et al., (14) analysed ICT response for T4b tumours, in which the efficacy between 2 drug regimen and 3 drug regimen was not statistically significant. The distribution of patients in our study was almost equal, with more patients enrolled in TPF (55% versus 45% in TPF and TP respectively). In the study by Noronha et al. (10) patients enrolled in the TPF arm (8.98% of the total sample size) were significantly less as compared to our study. This could be the reason for favourable response rate to TPF in Noronha et al. (10)

The toxicity profile when comparing two arms was drastically different in both arms. The toxicities were evaluated using the CTCAE 5.0 version. 20% in the TP arm had significant toxicities as compared to 83.33% in the TPF arm.

It was observed that TPF caused severe toxicities that could be potentially life threatening. On the other hand, TP caused negligible toxicities.

The results of this study cannot be considered statistically significant as because of the time constraints of the study. The sample size was also inadequate as it could not be reached due to COVID 19 pandemic, which was present during majority of the duration of the study.

However, even though the sample size was not reached, overall, the results were in favour of TP as induction therapy versus TPF. The efficacy of both regimens was similar, however the toxicity profile of TPF was severe compared to TP.

The TPF regimen is considered a standard regimen for ICT in locally advanced head and neck cancers. It is associated with severe toxicities, especially in the Indian population. Multiple factors contribute for this. It can be attributed to the unique genetic make-up and the clinicoepidemiological profile of Indian population. The TPF regimen requires robust support with GCSF and proper nutritional support and admission for administration of chemotherapy. Patients that present to our centre are nutritionally deficient, belong to lower socio-economic strata, which often makes it logistically difficult to deliver chemotherapy. Thus, there is need for an alternate regimen or altered dose of the TPF regimen that is suitable for Indian population.

Study by Noronha et al.(10) and Patil et al. (13)explores 2 drug regimens with TPF. Noronha et al.(10) inferred that TPF regimen is more effective and should not be substituted by TP unless the patient is otherwise unfit. Patil et al. (13) also concluded the same.

As studied by Tausif et al., (15) a weekly TPF regimen as compared to 3 weekly TPF regimen showed better tolerance with similar efficacy.

Treatment failures are more common with advanced diseases with patients have a greater than 50% risk of recurrence or development of distant metastatic disease. (16) Therefore, the total duration of treatment and delay in between different modalities, in a multimodality treatment can often lead to recurrences and disease failure. (17) Thus, surgeons should also be judicious in assessing patients for operability, as delay of treatment due to post operative complications renders all interventions ineffective and it also causes deterioration in the quality of life of the patient. Pre and post operative care is necessary for decreasing complications and recovery of the patient. (18)

Thus, one can conclude, the more aggressive the treatment is, the more there is response, but also more are the toxicities. It is thus imperative to choose an ICT regimen according to clinicoepidemiological profile, the performance status and the disease. More studies to develop a chemotherapy regimen that is suitable for Indian population like introducing a weekly TPF regimen could possibly be a solution to the conundrums that are faced due to the conventional TPF regimen. The limitations of this study are that it has not reached the adequate sample size. This is due to a limited time span with most of the study being conducted during the COVID 19 pandemic. However, it provides an insight into the toxicity profile of TPF regimen and the efficacy of TP regimen. Thus, TP regimen can be considered in patients whose disease is not particularly aggressive, is in the earlier strata of advanced diseases and in patients with low performance score.

V. CONCLUSION

ICT is still an evolving treatment option in advanced head and neck cancers with encouraging results. A common consensus needs to be reached for a chemotherapy regimen that is suitable to the clinico-epidemiological profile, the build and the genetic make-up of the Indian population. TPF is an established ICT regimen with favourable results but associated with a severe toxicity profile in Indian population. A weekly TPF regimen or TP can be used in patients with a low performance score, poor built, old age and associated comorbidities. In conclusion, ICT regimen should be individualized according to the patient condition to provide maximum benefits with minimum side effects and a better quality of life.

REFERENCES:

[1]. Mathur P, Sathishkumar K, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, Nallasamy V, John A, Narasimhan S, Roselind FS; ICMR-NCDIR-NCRP Investigator Group. Cancer Statistics, 2020: Report From National Cancer Registry Programme, India. JCO Glob Oncol. 2020 Jul;6:1063-1075. doi: 10.1200/GO.20.00122. PMID: 32673076; PMCID: PMC7392737.

[2]. Kulkarni MR. Head and Neck Cancer Burden in India. Int J Head and Neck Surg 2013;4(1):29-35

[3]. Perez, Brady 2019, Principles and Practice of Radiation Oncology, 9th edition, wolter'sklower

[4]. https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf
[5]. Prabhash K, Babu G, Chaturvedi P, Kuriakose M, Birur P, Anand AK, Kaushal A, Mahajan A, Syiemlieh J, Singhal M, Gairola M, Ramachandra P, Goyal S, John S, Nayyar R, Patil VM, Rao V, Roshan V, Rath GK. Indian clinical practice consensus guidelines for the management of squamous cell carcinoma of head and neck. Indian J Cancer. 2020 Feb;57(Supplement):S1-S5. doi: 10.4103/0019-509X.278971. PMID: 32167063.
[6]. Haddad RI, Posner M, Hitt R, Cohen EEW, Schulten J, Lefebvre JL, Vermorken JB. Induction chemotherapy in locally advanced squamous cell carcinoma of the head and neck: role, controversy, and future directions. Ann Oncol. 2018 May 1;29(5):1130-1140. doi: 10.1093/annonc/mdy102. PMID: 29635316; PMCID: PMC5961254.
[7]. Blanchard P, Bourhis J, Lacas B et al. Taxane-cisplatin-fluorouracil as induction chemotherapy in locally advanced head and neck cancers: an individual patient data meta-analysis of the meta-analysis of chemotherapy in head and neck cancer group. J Clin Oncol 2013; 31(23): 2854
[8]. Vermorken JB, Remenar E, van Herpen C et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007; 357(17): 1695–1704
[9]. Posner MR, Hershock DM, Blajman CR et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007; 357(17): 1705–1715.
[10]. Noronha V, Patil V, Joshi A, Muddu V, Bhattacharjee A, Juvekar S, Arya S, Chaturvedi P, Chaukar D, Pai PS, Dcruz AK, Prabhash K. Is taxane/platinum/5 fluorouracil superior to taxane/platinum alone and does docetaxel trump paclitaxel in induction therapy for locally advanced oral cavity cancers? Indian J Cancer. 2015 Jan -Mar;52(1):70-3. doi: 10.4103/0019-509X.175604. PMID: 26837979. 17
[11]. Clinical Practice Guidelines in Oncology (NCCN Guidelines TM).Head and Neck Cancers. Version 1.2017, https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf
[12]. Department of Veterans Affairs Laryngeal Cancer Study Group, Wolf GT, Fisher SG, Hong WK, Hillman R, Spaulding M, Laramore GE, Endicott JW, McClatchey K, Henderson WG. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med. 1991 Jun 13;324(24):1685-90. doi: 10.1056/NEJM199106133242402. PMID: 2034244.
[13]. Patil VM, Noronha V, Joshi A, Muddu VK, Gulia S, Bhosale B, Arya S, Juvekar S, Chatturvedi P, Chaukar DA, Pai P, D'cruz A, Prabhash K. Induction chemotherapy in technically unresectable locally advanced oral cavity cancers: does it make a difference? Indian J Cancer. 2013 Jan-Mar;50(1):1-8. doi: 10.4103/0019-509X.112263. Erratum in: Indian J Cancer. 2013 Apr-Jun;50(2):153. Joshi, Amit [added]. PMID: 23713035.
[14]. Joshi A, Patil VM, Noronha V, Juvekar S, Deshmukh A, Chatturvedi P, Chaukar DA, Agarwal JP, Ghosh S, Murthy V, D'cruz A, Prabhash K. Is there a role of induction chemotherapy followed by resection in T4b oral cavity cancers? Indian J Cancer. 2013 Oct-Dec;50(4):349-55. doi: 10.4103/0019-509X.123627. PMID: 24369216.
[15]. TousifDevale, SarathyVinu, Kumar Rajesh, Naik Radheshyam. Randomized Controlled Study Comparing Efficacy and Toxicity of Weekly vs. 3-Weekly Induction Chemotherapy in Locally Advanced Head and Neck Squamous Cell Carcinoma; Frontiers in Oncology, VOLUME=10 YEAR=2020 DOI=10.3389/fonc.2020.01284
[16]. Maria J Worsham (2011) Identifying the risk factors for late-stage head and neck cancer, Expert Review of Anticancer Therapy, 11:9, 1321-1325, DOI: 10.1586/era.11.135
[17]. Ang KK, Trotti A, Brown BW, Garden AS, Foote RL, Morrison WH, Geara FB, Klotch DW, Goepfert H, Peters LJ. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2001 Nov 1;51(3):571-8. doi: 10.1016/s0360-3016(01)01690-x. PMID: 11597795
[18]. Baehring E, McCorkle R. Postoperative complications in head and neck cancer. Clin J Oncol Nurs. 2012 Dec;16(6):E203-9. doi: 10.1188/12.CJON.E203-E209. PMID: 23178363.