

Therapeutic options in unresectable oral squamous cell carcinoma: a systematic review

Supplementary material 1. Search strategies

MEDLINE PubMed 12/04/2021	<p>#1 (((((((((((((((((((((((((((("Mouth Neoplasms"[Mesh] OR (oral carcinoma*[tiab] OR (oral[ti] AND carcinoma*[ti])) OR (oral cancer*[tiab] OR (oral[ti] AND cancer*[ti])) OR (oral tumor*[tiab] OR (oral[ti] AND tumor*[ti])) OR (oral tumour*[tiab] OR (oral[ti] AND tumour*[ti])) OR (oral neoplasm*[tiab] OR (oral[ti] AND neoplasm*[ti])) OR (oral oncolog*[tiab] OR (oral[ti] AND oncolog*[ti])) OR (oral malignan*[tiab] OR (oral[ti] AND malignan*[ti])) OR (mouth carcinoma*[tiab] OR (mouth[ti] AND carcinoma*[ti])) OR (mouth cancer*[tiab] OR (mouth[ti] AND cancer*[ti])) OR (mouth tumor*[tiab] OR (mouth[ti] AND tumor*[ti])) OR (mouth tumour*[tiab] OR (mouth[ti] AND tumour*[ti])) OR (mouth neoplasm*[tiab] OR (mouth[ti] AND neoplasm*[ti])) OR (mouth oncolog*[tiab] OR (mouth[ti] AND oncolog*[ti])) OR (mouth malignan*[tiab] OR (mouth[ti] AND malignan*[ti])) OR (buccal carcinoma*[tiab] OR (buccal[ti] AND carcinoma*[ti])) OR (buccal cancer*[tiab] OR (buccal[ti] AND cancer*[ti])) OR (buccal tumor*[tiab] OR (buccal[ti] AND tumor*[ti])) OR (buccal tumour*[tiab] OR (buccal[ti] AND tumour*[ti])) OR (buccal neoplasm*[tiab] OR (buccal[ti] AND neoplasm*[ti])) OR (buccal oncolog*[tiab] OR (buccal[ti] AND oncolog*[ti])) OR (buccal malignan*[tiab] OR (buccal[ti] AND malignan*[ti])) OR (oral cavity carcinoma*[tiab] OR (oral cavity[ti] AND carcinoma*[ti])) OR (oral cavity cancer*[tiab] OR (oral cavity[ti] AND cancer*[ti])) OR (oral cavity tumor*[tiab] OR (oral cavity[ti] AND tumor*[ti])) OR (oral cavity tumour*[tiab] OR (oral cavity[ti] AND tumour*[ti])) OR (oral cavity neoplasm*[tiab] OR (oral cavity[ti] AND neoplasm*[ti])) OR (oral cavity oncolog*[tiab] OR (oral cavity[ti] AND oncolog*[ti])) OR (oral cavity malignan*[tiab] OR (oral cavity[ti] AND malignan*[ti])) 90,682</p> <p>#2 (Unresectable[tiab] OR (Advanced[tiab] OR (Inoperable[tiab] 480,027</p> <p>#3 "Therapeutics"[Mesh] OR (Treatment*[tiab] OR (Management*[tiab] OR (Therap*[tiab] 9,862,814</p> <p>#4 #1 AND #2 AND #3 5,509</p> <p>#5 Filtered by last ten years 1896</p>
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Supplementary material 2. List of excluded studies and reasons for exclusion

Studies no specified for unresectable oral cancer (wrong population)

1. Chen LA, Anker CJ, Hunt JP, Buchmann LO, Grossmann KF, Boucher K, Fang LM, Shrieve DC, Hitchcock YJ. Clinical outcomes associated with evolving treatment modalities and radiation techniques for base-of-tongue carcinoma: thirty years of institutional experience. *Cancer Med*. 2015 May;4(5):651-60. doi: 10.1002/cam4.364.
2. Hauswald H, Zwicker F, Rochet N, Jensen AD, Debus J, Lindel K. Treatment of squamous cell carcinoma of the mobile tongue or tongue margins: an interdisciplinary challenge. *Acta Oncol*. 2013 Jun;52(5):1017-21. doi: 10.3109/0284186X.2012.722678.
3. Hoffmann C, Calugaru V, Borcoman E, Moreno V, Calvo E, Liem X, Salas S, Doger B, Jouffroy T, Mirabel X, Rodriguez J, Chilles A, Bernois K, Dimitriu M, Fakhry N, Hee Kam SW, Le Tourneau C. Phase I dose-escalation study of NBTXR3 activated by intensity-modulated radiation therapy in elderly patients with locally advanced squamous cell carcinoma of the oral cavity or oropharynx. *Eur J Cancer*. 2021 Mar;146:135-144. doi: 10.1016/j.ejca.2021.01.007.
4. Kartini D, Taher A, Panigoro SS, Setiabudy R, Jusman SW, Haryana SM, Abdullah M, Rustamadji P, Purwanto DJ, Sutandyo N, Suroyo I, Siregar BH, Maruli H, Sungkar S. Effect of melatonin supplementation in combination with neoadjuvant chemotherapy to miR-210 and CD44 expression and clinical response improvement in locally advanced oral squamous cell carcinoma: a randomized controlled trial. *J Egypt Natl Canc Inst*. 2020 Feb 28;32(1):12. doi: 10.1186/s43046-020-0021-0.
5. Kotsuma T, Yamazaki H, Masui K, Yoshida K, Shimizutani K, Akiyama H, Murakami S, Isohashi F, Yoshioka Y, Ogawa K, Tanaka E. Brachytherapy for Buccal Cancer: From Conventional Low Dose Rate (LDR) or Mold Technique to High Dose Rate Interstitial Brachytherapy (HDR-ISBT). *Anticancer Res*. 2017 Dec;37(12):6887-6892. doi: 10.21873/anticancer.12151.
6. Lambert A, Nees L, Nuyts S, Clement P, Meulemans J, Delaere P, Vander Poorten V. Photodynamic Therapy as an Alternative Therapeutic Tool in Functionally Inoperable Oral and Oropharyngeal Carcinoma: A Single Tertiary Center Retrospective Cohort Analysis. *Front Oncol*. 2021 Mar 4;11:626394. doi: 10.3389/fonc.2021.626394.
7. León X, García J, López M, Farré N, Majercakova K, Gallego Ó, López-Pousa A, Quer M. Organ preservation after treatment with induction chemotherapy in patients with locally advanced carcinomas (T3-T4) of oral cavity and oropharynx. *Acta Otorrinolaringol Esp (Engl Ed)*. 2021 Jan-Feb;72(1):27-36. English, Spanish. doi: 10.1016/j.otorri.2020.01.001.
8. Maggiore RJ, Curran EK, Witt ME, Haraf DJ, Vokes EE, Cohen EE. Survival and selected outcomes of older adults with locally advanced head/neck cancer treated with chemoradiation therapy. *J Geriatr Oncol*. 2013 Oct;4(4):327-33. doi: 10.1016/j.jgo.2013.05.003.
9. Meng J, Wang X, Zhuang QW, Gu QP, Zhang J, Li ZP. Clinical effectiveness of 125I-seed implantation in combination with nimotuzumab therapy for the advanced oral carcinoma: preliminary results. *Eur Rev Med Pharmacol Sci*. 2014;18(21):3304-10.
10. Mitsudo K, Koizumi T, Iida M, Iwai T, Oguri S, Yamamoto N, Itoh Y, Kioi M, Hirota M, Tohnai I. Thermochemoradiation therapy using superselective intra-arterial infusion via superficial temporal and occipital arteries for oral cancer with N3 cervical lymph node metastases. *Int J Radiat Oncol Biol Phys*. 2012 Aug 1;83(5):e639-45. doi: 10.1016/j.ijrobp.2012.02.057.
11. Naruse T, Yanamoto S, Matsushita Y, Sakamoto Y, Morishita K, Ohba S, Shiraishi T, Yamada SI, Asahina I, Umeda M. Cetuximab for the treatment of locally advanced and recurrent/metastatic oral cancer: An investigation of distant metastasis. *Mol Clin Oncol*. 2016 Aug;5(2):246-252. doi: 10.3892/mco.2016.928.
12. Nguyen-Tan PF, Zhang Q, Ang KK, Weber RS, Rosenthal DI, Soulieres D, Kim H, Silverman C, Raben A, Galloway TJ, Fortin A, Gore E, Westra WH, Chung CH, Jordan RC, Gillison ML, List M, Le QT. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. *J Clin Oncol*. 2014 Dec 1;32(34):3858-66. doi: 10.1200/JCO.2014.55.3925.
13. Nozato T, Koizumi T, Hayashi Y, Iida M, Iwai T, Oguri S, Hirota M, Kioi M, Koike I, Hata M, Tohnai I, Mitsudo K. Thermochemoradiotherapy Using Superselective Intra-arterial Infusion for Patients With Oral Cancer With Cervical Lymph Node Metastases. *Anticancer Res*. 2019 Mar;39(3):1365-1373. doi: 10.21873/anticancer.

14. Patil VM, Noronha V, Joshi A, Muddu VK, Gulia S, Bhosale B, Arya S, Juvekar S, Chaturvedi 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.
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19. Sher DJ, Thotakura V, Balboni TA, Norris CM Jr, Haddad RI, Posner MR, Lorch J, Goguen LA, Annino DJ, Tishler RB. Treatment of oral cavity squamous cell carcinoma with adjuvant or definitive intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys*. 2011 Nov 15;81(4):e215-22. doi: 10.1016/j.ijrobp.2011.02.023.
20. Tang X, Hu YJ, Ju WT, Fu Y, Sun WW, Liu Y, Tan YR, Wang LZ, Li J, Tu YY, Zhang CP, Zhang ZY, Zhong LP. Elevated growth differentiating factor 15 expression predicts long-term benefit of docetaxel, cisplatin and 5-fluorouracil induction chemotherapy in patients with oral cancer. *Oncol Lett*. 2018 May;15(5):8118-8124. doi: 10.3892/ol.2018.8324.
21. Tian Q, Zhu HH, Li H. Interstitial brachytherapy of oral squamous cell carcinoma with ultrasound-guided iodine-125 radioactive seed implantation. *Eur Rev Med Pharmacol Sci*. 2018 Mar;22(6):1680-1685. doi: 10.26355/eurev_201803_14580.

Wrong intervention

1. Oertel K, Spiegel K, Schmalenberg H, Dietz A, Maschmeyer G, Kuhnt T, Sudhoff H, Wendt TG, Guntinas-Lichius O. Phase I trial of split-dose induction docetaxel, cisplatin, and 5-fluorouracil (TPF) chemotherapy followed by curative surgery combined with postoperative radiotherapy in patients with locally advanced oral and oropharyngeal squamous cell cancer (TISOC-1). *BMC Cancer*. 2012 Oct 20;12:483. doi: 10.1186/1471-2407-12-483.
2. Patil VM, Chakraborty S, Shenoy PK, Manuprasad A, Sajith Babu TP, Shivkumar T, Babu S, Bhatteerjee A, Balasubramanian S. Tolerance and toxicity of neoadjuvant docetaxel, cisplatin and 5 fluorouracil regimen in technically unresectable oral cancer in resource limited rural based tertiary cancer center. *Indian J Cancer*. 2014 Jan-Mar;51(1):69-72. doi: 10.4103/0019-509X.134649.
3. Patil VM, Muttath G, Babu S, Kumar ST, Jones J, Sen S, Chakraborty S. Does the use of induction chemotherapy in oral cavity cancer compromise subsequent loco-regional treatment delivery: Results from a matched pair analysis. *Indian J Cancer*. 2015 Oct-Dec;52(4):632-6. doi: 10.4103/0019-509X.178442.
4. Rades D, Ulbricht T, Hakim SG, Schild SE. Cisplatin superior to carboplatin in adjuvant radiochemotherapy for locally advanced cancers of the oropharynx and oral cavity. *Strahlenther Onkol*. 2012 Jan;188(1):42-8. doi: 10.1007/s00066-011-0005-z.
5. Shin JY, Yoon JK, Shin AK, Diaz AZ. Locoregionally advanced oral cavity cancer: A propensity-score matched analysis on overall survival with emphasis on the impact of adjuvant radiotherapy. *Head Neck*. 2018 Sep;40(9):1934-1946. doi: 10.1002/hed.25185.
6. Sultania M, Deo SVS, Shukla NK, Sharma A, Sahoo R, Bhasker S. Low Cost, Low Dose, Oral, Neoadjuvant Chemotherapy Protocol in Locally Advanced Borderline Oral Cancers-Feasibility Study. *Indian J Surg Oncol*. 2021 Mar;12(1):67-72. doi: 10.1007/s13193-020-01247-8.
7. Veluthattil AC, Sudha SP, Kandasamy S, Chakkalakkoombil SV. Effect of Hypofractionated, Palliative Radiotherapy on Quality of Life in Late-Stage Oral Cavity Cancer: A Prospective Clinical Trial. *Indian J Palliat Care*. 2019 Jul-Sep;25(3):383-390. doi: 10.4103/IJPC.IJPC_115_18.

Wrong study design

1. Furness S, Glenny AM, Worthington HV, Pavitt S, Oliver R, Clarkson JE, Macluskey M, Chan KK, Conway DI. Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy. *Cochrane Database Syst Rev.* 2011 Apr 13;(4):CD006386. doi: 10.1002/14651858
2. Kaul P, Singh MP, Pasricha R, Garg PK. Methotrexate based oral chemotherapy for advanced oral cancer during COVID-19 pandemic: Another option in the therapeutic armamentarium. *Oral Oncol.* 2020 Aug;107:104839. doi: 10.1016/j.oraloncology.2020.104839.
3. Rehman A, Allaudin Z, Nisar H, Khan IU, Fatima I, Shami A, Masood M, Shahid A. Efficacy and Toxicity of Concurrent Chemoradiation in Inoperable Oral Carcinoma in Pakistani Population. *J Coll Physicians Surg Pak.* 2017 Jun;27(6):342-347.

Other reasons

1. Dequanter D, Shahla M, Aubert C, Deniz Y, Lothaire P. Chemoradiation for advanced oral and (pharyngo) laryngeal carcinoma: single institution outcome analysis. *Minerva Stomatol.* 2015 Jun;64(3):111-5.
2. Janmunee N, Peerawong T, Rordlamool P, Bridthikitti J, Tangthongkum M, Kongkamol C, Hirunpat S. Tumor volume as a prognostic factor on the median survival in locally advanced oral cancer treated with definitive chemoradiotherapy. *Indian J Cancer.* 2021 Jan 27. doi: 10.4103/ijc.IJC_86_20.
3. 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.
4. Vedesoundaram P, Prasanna AK, Ks R, Selvarajan G, Sinnatamby M, Ramapandian S, Kandasamy S. Role of high dose rate interstitial brachytherapy in early and locally advanced squamous cell carcinoma of buccal mucosa. *Springerplus.* 2014 Oct 9;3:590. doi: 10.1186/2193-1801-3-590.

Supplementary material 3. Characteristics of the included studies

Author and year	Design	Country	Language	Sample size	Sample features	Risk factors
Bazyka 2019	RCT	Ukraine	English Ukrainian	280	Age: NR F: NR M: NR	NR
Biswas 2019	P. Cohort	India	English	61	Age: NR F: NR M: NR	NR
Chang 2017	CT	Taiwan	English	43	Age: 18-70 Y F: 4 M: 39	Alcohol 74% Betel nut 72% Smoking 79%
Chhatui 2015	RCT	India	English	50	Age: 19-65 Y F: 11 M: 39	NR
Chitapanarux 2017	R. Cohort	Thailand	English	775	Age: 54-74 Y F: 316 M: 459	Alcohol 68% Betel nut 28% Smoking 81%
Donato 2013	P. Cohort	Italy	English	24	Age: 45-85 Y F: 9 M: 15	NR
Elbers 2017	R. Cohort	Netherlands	English	209	Age: 62.0 Y F: 72 M: 137	Alcohol 42% Smoking 53.6%
Foster 2018	R. Cohort	United States	English	140	Age: 27-80 Y F: 44 M: 96	NR
Hayashi 2019	R. Cohort	Japan	English	46	Age: 39-85 Y F: 25 M: 21	Smoking 83%
Hino 2011	RCT	Japan	English	16	Age: 73.5 Y F: 5 M: 11	NR
Iqbal 2015	R. Cohort	Pakistan	English	63	Age: 24-77 Y F: 19 M: 44	Alcohol 0% Betel nut 46% Smoking 43% Tobacco chew 27%
Larizadeh 2012	P. Cohort	Iran	English	69	Age: 27-87 Y F: 29 M: 40	NR
Li 2014	RCT	China	English	99	Age: 57.1 Y F: 38 M: 61	NR
Meng 2014	RCT	China	English	17	Age: 54-89 Y F: 7 M: 10	NR
Murakami 2017	P. Cohort	Japan	English	47	Age: 45-91 Y F: 23 M: 24	NR
Oyama 2020	P. Cohort	Japan	English	37	Age: 26-79 Y F: 6 M: 31	NR
Patil 2014	R. Cohort	India	English	721	Age: 22-78 Y F: 106 M: 615	Alcohol 37.5% Betel nut 81.5% Smoking 53.8% Tobacco 69.1%

Author and year	Design	Country	Language	Sample size	Sample features	Risk factors
Pederson 2011	P. Cohort	United States	English	21	Age: 34-81 Y F: 4 M: 17	Alcohol 95.2% Smoking 76.2%
Rewadkar 2017	R. Cohort	India	English	50	Age: 20-70 Y F: 13 M: 37	Tobacco + alcohol 18% Tobacco + chewing 34% Tobacco + smoking 48%
Rudresha 2017a	R. Cohort	India	English	80	Age: 34-62 Y F: 22 M: 58	Smoking 66.3% Tobacco/betel 88.7%
Rudresha 2017b	R. Cohort	India	English	116	Age: 31-62 Y F: 26 M: 90	Smoking 53.4% Tobacco/betel 92.2%
Santos 2017	R. Cohort	Spain	English	24	Age: 60.0 Y F: 4 M: 20	NR
Sato 2019	R. Cohort	Japan	English	17	Age: 44-87 Y F: 3 M: 14	NR
Scher 2015	R. Cohort	United States	English	73	Age: 35-89 Y F: 34 M: 39	Smoking 90.4%
Shia 2020	R. Cohort	Taiwan	English	976	Age: ≥70 Y F: 159 M: 817	Alcohol 70% Betel nut 87.9% Smoking 70.3%
Singh 2013	RCT	India	English	60	Age: 40-65 Y F: 15 M: 45	Tobacco 88.3%
Takácsi-Nagy 2013	P. Cohort	Hungary	English	60	Age: 36-78 Y F: 10 M: 50	NR
Takayama 2016	CT	Japan	English	33	Age: 25-69 Y F: 11 M: 22	NR
Vedasoundaram 2020	P. Cohort	India	English	125	Age: 32-73 Y F: 48 M: 77	Alcohol 16% Alcohol + tobacco 12% Tobacco + smoking 47.2%
Wu 2014	R. Cohort	Taiwan	English	21	Age: 39-75 Y F: 2 M: 19	NR
Yen 2019	CT	Taiwan	English	47	Age: 34-66 Y F: 1 M: 46	NR
Zaidi 2020	CT	Pakistan	English	35	Age: 18-65 Y F: 11 M: 24	NR
Zhang 2013	R. Cohort	Canada	English	222	Age: 16-95 Y F: 88 M: 133	NR

Abbreviations: CT, clinical trial; F, female; M, male; NR, not reported; P, prospective; R, retrospective; RCT, randomized controlled trial; Y, years.