# Chemioterapia di induzione con docetaxel, cisplatino e 5FU seguita da chirurgia e radioterapia postoperatoria vs immediata chirurgia e RT postoperatoria nei carcinomi squamosi del cavo orale. Studio randomizzato di fase III.

*(a cura di A. Testolin - Belluno)*

## Randomized Phase III Trial of Induction Chemotherapy With Docetaxel, Cisplatin, and Fluorouracil Followed by Surgery Versus Up-Front Surgery in Locally Advanced Resectable Oral Squamous Cell Carcinoma

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ABSTRACT

**Purpose**
To evaluate induction chemotherapy with docetaxel, cisplatin, and fluorouracil (TPF) followed by surgery and postoperative radiotherapy versus up-front surgery and postoperative radiotherapy in patients with locally advanced resectable oral squamous cell carcinoma (OSCC).

**Patients and Methods**
A prospective open-label phase III trial was conducted. Eligibility criteria included untreated stage III or IVA locally advanced resectable OSCC. Patients received two cycles of TPF induction chemotherapy (docetaxel 75 mg/m$^2$ on day 1, cisplatin 75 mg/m$^2$ on day 1, and fluorouracil 750 mg/m$^2$ on days 1 to 5) followed by radical surgery and postoperative radiotherapy (54 to 66 Gy) versus up-front radical surgery and postoperative radiotherapy. The primary end point was overall survival (OS). Secondary end points included local control and safety.

**Results**
Of the 256 patients enrolled onto this trial, 222 completed the full treatment protocol. There were no unexpected toxicities, and induction chemotherapy did not increase perioperative morbidity. The clinical response rate to induction chemotherapy was 80.6%. After a median follow-up of 30 months, there was no significant difference in OS (hazard ratio [HR], 0.977; 95% CI, 0.634 to 1.507; $P = .918$) or disease-free survival (HR, 0.974; 95% CI, 0.654 to 1.45; $P = .897$) between patients treated with and without TPF induction. Patients in the induction chemotherapy arm with a clinical response or favorable pathologic response (≤ 10% viable tumor cells) had superior OS and locoregional and distant control.

**Conclusion**
Our study failed to demonstrate that TPF induction chemotherapy improves survival compared with up-front surgery in patients with resectable stage III or IVA OSCC.

Commento.

Sono stati pubblicati i risultati di studio randomizzato di fase III (attivato nel 2008 e chiuso nel 2010) che prevedeva il confronto tra chemioterapia (CT) di induzione con docetaxel, cisplatino e 5FU (TPF) seguita da chirurgia e RT postoperatoria vs immediata chirurgia e RT postoperatoria nei carcinomi squamosi del cavo orale.

Sono stati randomizzati un totale di 256 pazienti (128 per braccio). La chemioterapia di induzione prevedeva la somministrazioni di 2 cicli di TPF. La RT postoperatoria è stata eseguita con tecnica conformazionale o ad intensità modulata a dosi totali di 54-60 Gy in assenza di fattori di rischio o 66 Gy se margini chirurgici positivi o estensione extracapsulare linfonodale o in presenza di invasione vascolare. Le caratteristiche cliniche dei pazienti sono riportate nella tabella sottostante.

**Table 1.** Baseline Patient Demographic and Clinical Characteristics

| Characteristic | Total (N = 256) No. | % | Control Arm (n = 128) No. | % | Experimental Arm (n = 128) No. | % | P* |
|---|---|---|---|---|---|---|---|
| Sex | | | | | | | .683 |
| Male | 179 | 69.9 | 88 | 68.8 | 91 | 71.1 | |
| Female | 77 | 30.1 | 40 | 31.2 | 37 | 28.9 | |
| Age, years | | | | | | | .792 |
| Median | 55 | | 56 | | 55 | | |
| Range | 26-75 | | 26-75 | | 29-74 | | |
| < 60 | 168 | 65.6 | 85 | 66.4 | 83 | 64.8 | |
| ≥ 60 | 88 | 34.4 | 43 | 33.6 | 45 | 35.2 | |
| Site | | | | | | | .509 |
| Tongue | 113 | 44.1 | 60 | 46.9 | 53 | 41.4 | |
| Buccal | 45 | 17.6 | 20 | 15.6 | 25 | 19.5 | |
| Gingiva | 40 | 15.6 | 19 | 14.8 | 21 | 16.4 | |
| Floor of mouth | 30 | 11.7 | 18 | 14.1 | 12 | 9.4 | |
| Palate | 18 | 7.0 | 6 | 4.7 | 12 | 9.4 | |
| Retromolar trigone | 10 | 3.9 | 5 | 3.9 | 5 | 3.9 | |
| T stage | | | | | | | .299 |
| T1 | 9 | 3.5 | 6 | 4.7 | 3 | 2.3 | |
| T2 | 57 | 22.3 | 27 | 21.1 | 30 | 23.4 | |
| T3 | 149 | 58.2 | 79 | 61.7 | 70 | 54.7 | |
| T4 | 41 | 16.0 | 16 | 12.5 | 25 | 19.5 | |
| N stage | | | | | | | .294 |
| N0 | 110 | 43.0 | 61 | 47.7 | 49 | 38.3 | |
| N1 | 94 | 36.7 | 42 | 32.8 | 52 | 40.6 | |
| N2 | 52 | 20.3 | 25 | 19.5 | 27 | 21.1 | |
| Disease stage | | | | | | | .223 |
| III | 177 | 69.1 | 93 | 72.7 | 84 | 65.6 | |
| IVA | 79 | 30.9 | 35 | 27.3 | 44 | 34.4 | |
| Pathologic differentiation | | | | | | | .902 |
| Well | 80 | 31.2 | 38 | 29.7 | 42 | 32.8 | |
| Moderate | 165 | 64.5 | 85 | 66.4 | 80 | 62.5 | |
| Poor | 11 | 4.3 | 5 | 3.9 | 6 | 4.7 | |
| Smoking status† | | | | | | | .134 |
| Current/former | 126 | 49.2 | 57 | 44.5 | 69 | 53.9 | |
| Never | 130 | 50.8 | 71 | 55.5 | 59 | 46.1 | |
| Alcohol use‡ | | | | | | | .440 |
| Positive | 98 | 40.6 | 46 | 39.8 | 52 | 41.4 | |
| Negative | 158 | 59.4 | 82 | 60.2 | 76 | 58.6 | |

*P value from $\chi^2$ test was reported to compare baseline characteristics between the two treatment arms.
†Former/current smokers defined as ≥ one pack-year history of smoking.
‡Positive alcohol use was defined as current alcohol use of > one drink per day for 1 year (12 oz of beer with 5% alcohol, 5 oz of wine with 12% to 15% alcohol, or 1 oz of liquor with 45% to 60% alcohol). All other patients were classified as negative alcohol users.

Sinteticamente i risultati clinici possono essere così riassunti:

**Risposta alla chemioterapia di induzione**: risposta clinica completa 8.1% (10 pazienti) risposta clinica parziale 72.6% (90 pazienti). Risposta patologica favorevole (secondo criteri proposti da Licitra et al. J Clin Oncol 21:327-333, 2003) 27.7% (33 pazienti inclusi 16 con risposta patologica completa).

**Sopravvivenza:** nessuna differenza relativamente alla sopravvivenza globale o libera da malattia (vedi figure sottostanti). A 2 anni sopravvivenza globale del 68.2% nel gruppo di controllo e del 68.8% nel gruppo che ha effettuato chemioterapia di induzione. Sono deceduti 82 pazienti 42 nel gruppo di controllo e 40 nel gruppo sperimentale (vedi figura sottostante).

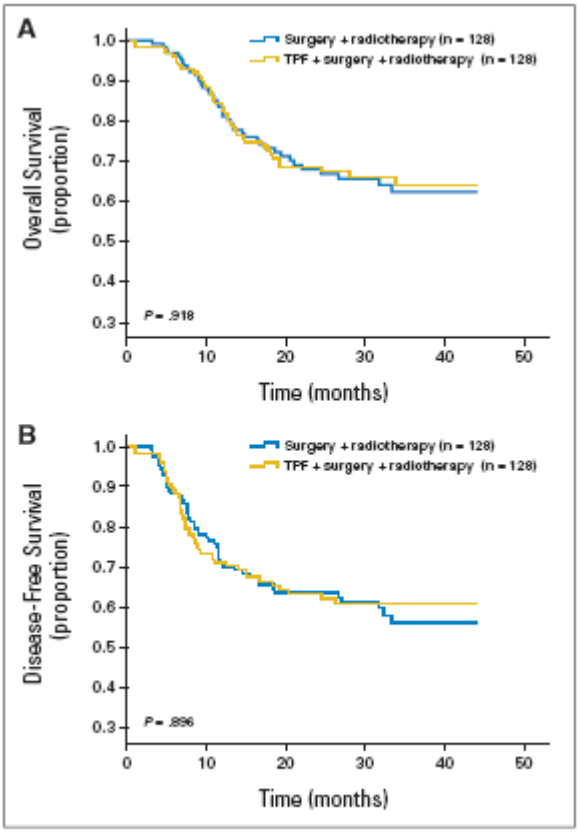


Fig 2. (A) Overall and (B) disease-free survival in the control and experimental arms. TPF, docetaxel, cisplatin, and fluorouracil.

**Ricadute loco regionali:** nessuna differenza nei due gruppi (30.5% nel gruppo di controllo e 31.3% nel gruppo sperimentale)

**Metastasi a distanza:** non significativa riduzione della sopravvivenza libera da metastasi anche se gli autori riportano un "trend positivo" nella riduzione della incidenza di metastasi a distanza nel gruppo sperimentale (5.5% vs 8.7%).

**"Exploratory subgroup analysis"**: prescindendo dalla correttezza di questo tipo di analisi, gli autori riportano un possibile beneficio sulla sopravvivenza esclusivamente nel sottogruppo di pazienti clinicamente N2 alla diagnosi trattati con chemioterapia di induzione.

**Tossicità:** gli autori riportano un 9% di tossicità di grado 3 correlata alla chemioterapia di induzione. La chemioterapia non ha determinato un incremento della morbidità chirurgica. Non differenze nei due gruppi di pazienti relativamente alla tossicità da radioterapia. Non sono stati riscontrati decessi correlati al trattamento.

**CONCLUSIONI.** La chemioterapia di induzione, con docetaxel, cisplatino e fluorouracile, non sembra determinare un aumento della sopravvivenza globale o libera da malattia nei pazienti con carcinoma squamoso del cavo orale trattati con chirurgia e radioterapia postoperatoria. Non determina inoltre una riduzione delle ricadute loco regionali. Gli autori riportano esclusivamente un "trend" positivo nella riduzione delle metastasi a distanza nel gruppo di pazienti trattati con chemioterapia.
I risultati di questo studio sembrano in linea con quelli preliminari degli studi DeCIDE e PARADIGM (in appendice riporto abstracts presentati all'ASCO 2012).
Se confermati, questi risultati potrebbero avere dei riflessi nella pratica clinica, visto che, almeno nella mia personale esperienza, la chemioterapia di induzione con schema TPF è sostanzialmente diventato uno….. standard terapeutico.

APPENDICE

# DeCIDE: A phase III randomized trial of docetaxel (D), cisplatin (P), 5-fluorouracil (F) (TPF) induction chemotherapy (IC) in patients with N2/N3 locally advanced squamous cell carcinoma of the head and neck (SCCHN).

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Abstract Disclosures

## Abstract

**5500**

**Background:** IC is associated with lower distant failure (DF) rates in SCCHN but an improvement in overall survival (OS) has not been validated. The goal of this trial was to determine whether IC prior to chemoradiotherapy (CRT) improves survival compared to CRT alone. **Methods:** In this phase 3, open-label trial, subjects with pathologically confirmed SCCHN; N2/N3 disease without metastases; no prior therapy; KPS ³ 70%; and intact organ function were randomized to CRT alone (CRT arm) [5 days of D (25 mg/m$^2$), F (600 mg/m$^2$), hydroxyurea (500 mg BID), and RT (150 cGy BID) followed by a 9 day break] or to 2 cycles of IC [D (75 mg/m$^2$), P (75 mg/m$^2$), F (750 mg/m$^2$ day 1-5)] followed by the same CRT (IC arm). Primary endpoint was OS. Secondary endpoints included DF free survival, failure pattern, and recurrence-free survival (RFS). 280 subjects provided 80% power to detect a hazard ratio HR=0.5 for OS (a=0.05). **Results:** 280 subjects were accrued from 2004-09 with minimum follow-up 24 months. Of 142 patients randomized to IC, 91% received 2 cycles and 87% continued to CRT. Treatment adherence during CRT was high for docetaxel and hydroxyurea, but fewer than 75% of the patients received target dose of 5FU in both arms. RT was delivered without major deviations in 94% and 95% of patients on IC and CRT arms, respectively. The most common grade 3-4 toxicities during IC were febrile neutropenia (9%) and mucositis (8%), and during CRT (both arms combined) they were mucositis (45%), dermatitis (19%), and leukopenia (17%). Only grade 3-4 leukopenia and neutropenia rates were significantly higher in IC (p=0.002 and p=0.02, respectively). Table shows efficacy. **Conclusions:** High survival rates were observed in both arms. Further analysis and follow-up may provide insight into why the significant decrease in DF did not translate into improved OS.

**3-year outcomes.**

| Endpoint | IC arm (%) | CRT arm (%) | HR | 95% CI | p value |
|---|---|---|---|---|---|
| OS | 75 | 73 | 0.92 | 0.59–1.42 | 0.70 |
| DF-free survival | 69 | 64 | 0.84 | 0.56–1.26 | 0.39 |
| RFS | 67 | 59 | 0.76 | 0.52–1.13 | 0.18 |
| Cumulative incidence of DF | 10 | 19 | 0.46 | 0.23–0.92 | 0.025 |
| Cumulative incidence of locoregional failure | 9 | 12 | 0.79 | 0.37–1.68 | 0.55 |

Abstract presentation from the 2012 ASCO Annual Meeting

# The PARADIGM trial: A phase III study comparing sequential therapy (ST) to concurrent chemoradiotherapy (CRT) in locally advanced head and neck cancer (LANHC).

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Abstract Disclosures

## Abstract

**5501**

**Background:** PARADIGM is a multicenter phase III study comparing TPF (docetaxel, cisplatin, and 5-fluorouracil)-based ST (Arm A) to upfront cisplatin CRT (Arm B) in patients (pts) with LAHNC. Pt accrual was terminated in 12/2008 due to slow enrollment with 145 of 300 planned analyzable patients accrued. Safety data was previously presented at the 2010 ASCO annual meeting showing no unusual pattern of toxicities in either arm. Here we present the survival results. **Methods:** Pts were randomized to receive arm A-ST (as induction chemotherapy (ICT) with TPF x 3) followed by CRT with either weekly carboplatin and once daily radiotherapy, or weekly docetaxel and accelerated boost radiotherapy based on adequate response to ICT; or arm B - accelerated boost CRT with bolus cisplatin x 2. The primary endpoint was survival. With original accrual target of 300 analyzable patients, this study was powered at 80% to detect an improvement in 3-year survival from 55% (arm B) to 70% (arm A). **Results:** A total of 145 previously untreated pts were enrolled (Arm A: 70; Arm B: 75), of whom 127 were male and 127 were Caucasian. Median age was 55; patients had PS of 0 (97) or 1 (48). Sites of disease were oropharynx: 80, larynx: 24, hypopharynx: 15, and oral cavity: 26. Disease stages were II (1 pt), III (20 pts) and IV (124 pts). After a median follow-up of 49 months, 41 pts have died (20 in arm A and 21 in arm B). Three-year survival was 73% (arm A) and 78% (arm B) (HR1.09; 95% CI 0.59 to 2.03 p=0.77). Three-year progression-free survival was 67% (arm A) and 73% (arm B) (HR 1.2; 95% CI 0.65 to 2.22; p=0.55). Patterns of failure will be presented at the meeting. **Conclusions:** Althoughthese results suggest no survival differences between CRT and ST for patients with LAHNC, the study was terminated before the planned accrual could be reached. HPV status for the oropharynx cases which represented the majority of patients was not available for stratification; and excellent survival was seen in both arms.

Abstract presentation from the 2012 ASCO Annual Meeting