Nuovo sistema di stadiazione dei tumori HPV-correlati

Proposed Staging System for Patients With HPV-Related Oropharyngeal Cancer Based on Nasopharyngeal Cancer N Categories

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A B S T R A C T

Purpose
Patients with human papillomavirus (HPV)–related oropharyngeal cancer (OPC) generally present with more advanced disease but have better survival than patients with HPV-unrelated OPC. The current American Joint Commission on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM staging system for OPC was developed for HPV-unrelated OPC. A new staging system is needed to adequately predict outcomes of patients with HPV-related OPC.

Patients and Methods
Patients with newly diagnosed HPV-positive OPC (by p16 immunohistochemistry or in situ hybridization) treated at our institution from January 2003 through December 2012 were included. By using recursive partitioning analysis (RPA), we developed new stage groupings with both traditional OPC regional lymph node (N) categories and nasopharyngeal carcinoma (NPC) N categories. Survival was estimated by the Kaplan-Meier method, and the relationship between stage and survival was examined by using Cox proportional hazards regression analysis.

Results
A total of 661 patients with HPV-positive OPC met the inclusion criteria. With the traditional TNM staging system, there was no difference in survival between stages ($P = .141$). RPA with NPC N categories resulted in more balanced stage groups and better separation between groups for 5-year survival than RPA with traditional OPC N categories. With the stage groupings that were based in part on NPC N categories, the risk of death increased with increasing stage (P for trend $< .001$), and patients with stage III disease had five times the risk of death versus patients with stage IA disease.

Conclusion
New stage groupings that are based on primary tumor (T) categories and NPC N categories better separate patients with HPV-positive OPC with respect to survival than does the current AJCC/UICC TNM staging system. Although confirmation of our findings in other patient populations is needed, we propose consideration of NPC N categories as an alternative to the traditional OPC N categories in the new AJCC/UICC TNM staging system that is currently being developed.

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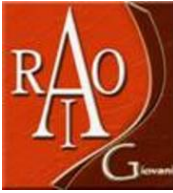
Nei pazienti affetti da tumori del testa-collo, il grado di coinvolgimento linfonodale loco-regionale è da sempre considerato uno dei principali fattori prognostici. Recentemente è stato altresì dimostrato come nei tumori dell'orofaringe i maggiori fattori ad impattare sulla prognosi dei pazienti siano la correlazione o meno con l'infezione da HPV e l'abitudine al fumo. Ad oggi il sistema di classificazione in uso non prevede distinzioni basate sullo status dell'HPV in questi tumori, non fornendo quindi criteri per formulare una prognosi accurata per i sottogruppi di pazienti. D'altra parte i tumori del rinofaringe presentano in larga parte una genesi correlata all'infezione da EBV (e quindi una storia clinica più assimilabile a quella dei pazienti affetti da tumori HPV-correlati) e criteri classificativi del coinvolgimento linfonodale diversi rispetti agli altri tumori del distretto testa-collo. Gli autori di questo studio hanno pertanto effettuato un'analisi retrospettiva su 661 pazienti affetti da tumori dell'orofaringe HPV-relati trattati nell'arco di un decennio. Attraverso l'utilizzo della recursive partitioning analysis (RPA) il grado di coinvolgimento linfonodale di questi pazienti è stato classificato sia utilizzando il sistema attualmente in uso che quello utilizzato per i tumori del rinofaringe.
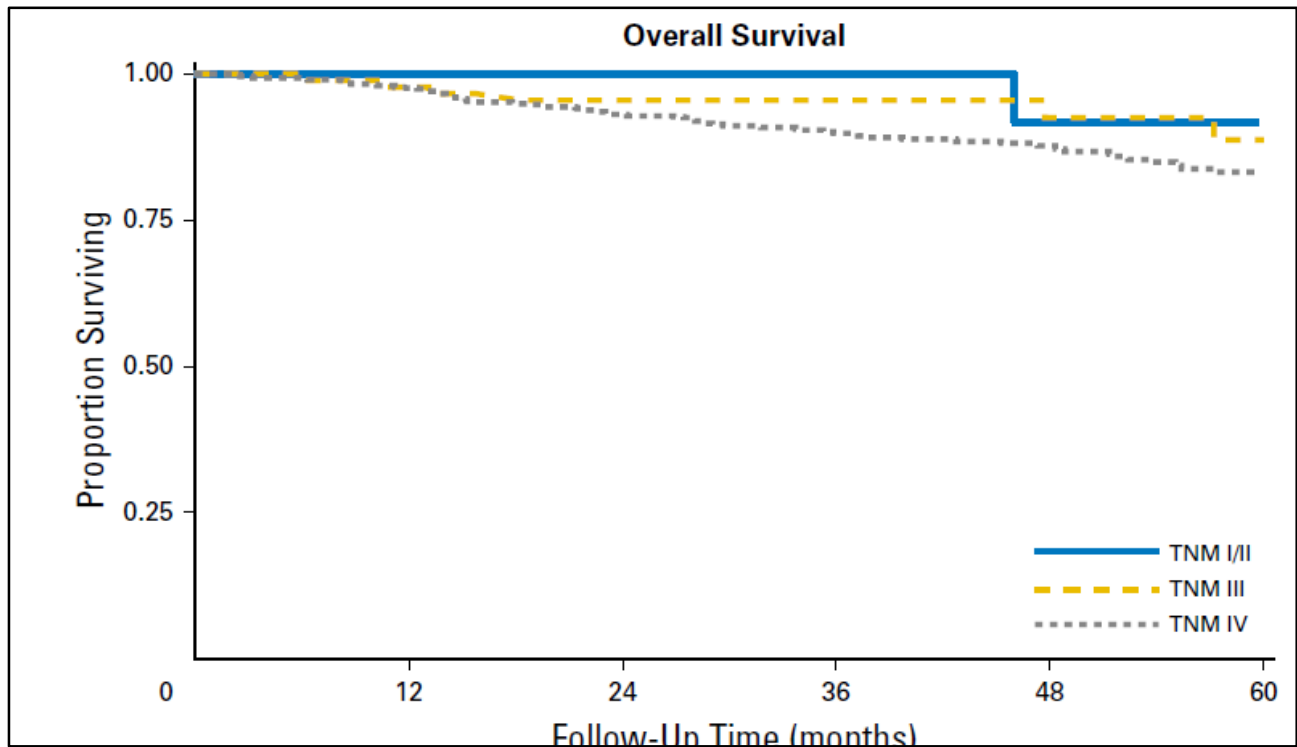

Utilizzando l'attuale sistema classificativo non si apprezzano differenze in termini di Overall Survival (OS) fra i vari sottogruppi di pazienti; la categoria **T** presenta un impatto significativo sulla sopravvivenza mentre la categoria **N** non vi influisce. Inoltre l'82% dei pazienti viene classificato come stadio IV.

Overall Survival
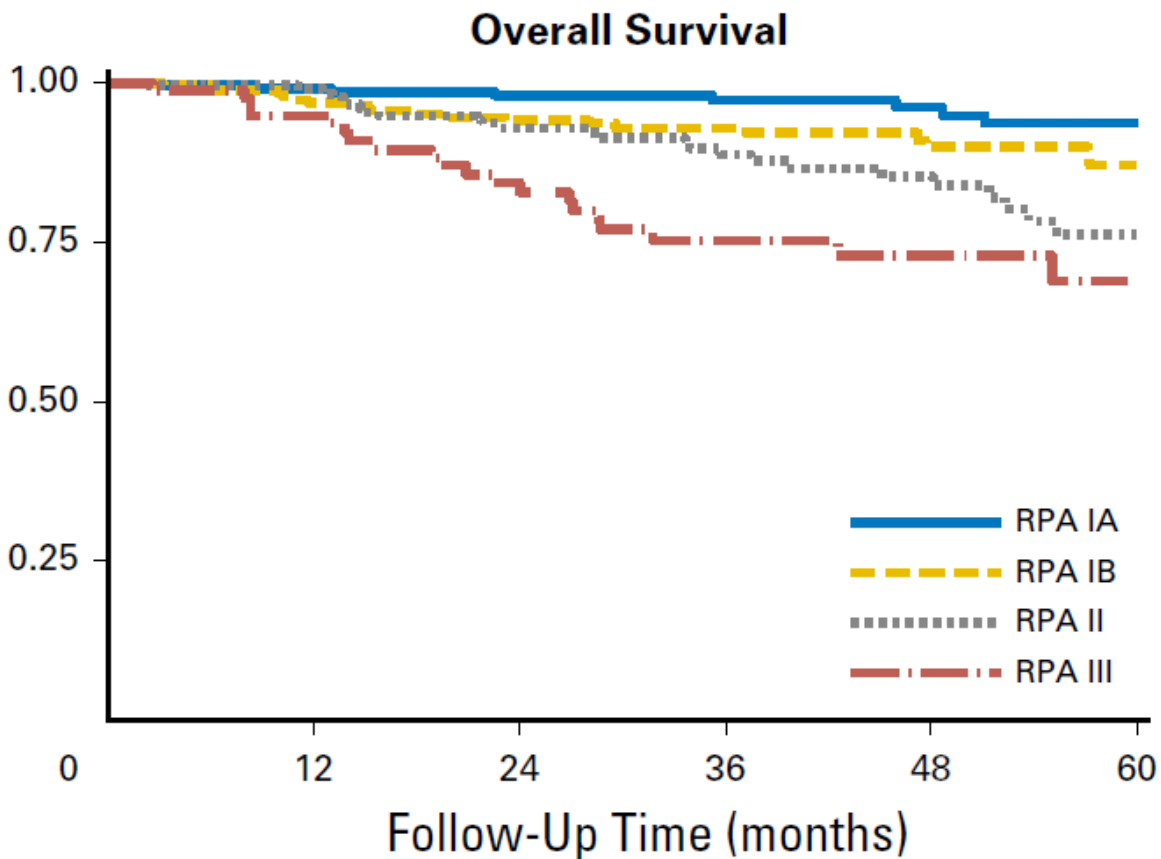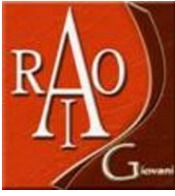
Riclassificando i pazienti secondo I criteri del tumore del rinofaringe anche la categoria **N** impatta sulla OS e sulla PFS. I pazienti inoltre vengono suddivisi in maniera più omogenea nella varie sotto-categorie.

Conclusioni

I tumori dell'orofaringe HPV-correlati presentano una differente storia clinica e prognosi che rende necessario quanto prima una diversa classificazione rispetto ai tumori fumo ed alcol-correlati. L'utilizzo dei criteri già adottati per i tumori del rinofaringe è in grado di suddividere prognosticamente questi pazienti in maniera più accurata.
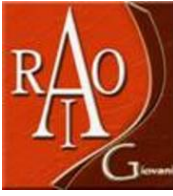
Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study

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Summary

Background Human papillomavirus-related (HPV+) oropharyngeal cancer is a rapidly emerging disease with generally good prognosis. Many prognostic algorithms for oropharyngeal cancer incorporate HPV status as a stratification factor, rather than recognising the uniqueness of HPV+ disease. The International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S) aimed to develop a TNM classification specific to HPV+ oropharyngeal cancer.

Methods The ICON-S study included patients with non-metastatic oropharyngeal cancer from seven cancer centres located across Europe and North America; one centre comprised the training cohort and six formed the validation cohorts. We ascertained patients' HPV status with p16 staining or in-situ hybridisation. We compared overall survival at 5 years between training and validation cohorts according to 7th edition TNM classifications and HPV status. We used recursive partitioning analysis (RPA) and adjusted hazard ratio (AHR) modelling methods to derive new staging classifications for HPV+ oropharyngeal cancer. Recent hypotheses concerning the effect of lower neck lymph nodes and number of lymph nodes were also investigated in an exploratory training cohort to assess relevance within the ICON-S classification.

Findings Of 1907 patients with HPV+ oropharyngeal cancer, 661 (35%) were recruited at the training centre and 1246 (65%) were enrolled at the validation centres. 5-year overall survival was similar for 7th edition TNM stage I, II, III, and IVA (respectively; 88% [95% CI 74–100]; 82% [71–95]; 84% [79–89]; and 81% [79–83]; global p=0·25) but was lower for stage IVB (60% [53–68]; p<0·0001). 5-year overall survival did not differ among N0 (80% [95% CI 73–87]), N1–N2a (87% [83–90]), and N2b (83% [80–86]) subsets, but was significantly lower for those with N3 disease (59% [51–69]; p<0·0001). Stage classifications derived by RPA and AHR models were ranked according to survival performance, and AHR-New was ranked first, followed by AHR-Orig, RPA, and 7th edition TNM. AHR-New was selected as the proposed ICON-S stage classification. Because 5-year overall survival was similar for patients classed as T4a and T4b, T4 is no longer subdivided in the re-termed ICON-S T categories. Since 5-year overall survival was similar among N1, N2a, and N2b, we re-termed the 7th edition N categories as follows: ICON-S N0, no lymph nodes; ICON-S N1, ipsilateral lymph nodes; ICON-S N2, bilateral or contralateral lymph nodes; and ICON-S N3, lymph nodes larger than 6 cm. This resembles the N classification of nasopharyngeal carcinoma but without a lower neck lymph node variable. The proposed ICON-S classification is stage I (T1–T2N0–N1), stage II (T1–T2N2 or T3N0–N2), and stage III (T4 or N3). Metastatic disease (M1) is classified as ICON-S stage IV. In an exploratory training cohort (n=702), lower lymph node neck involvement had a significant effect on survival in ICON-S stage III but had no effect in ICON-S stage I and II and was not significant as an independent factor. Overall survival was similar for patients with fewer than five lymph nodes and those with five or more lymph nodes, within all ICON-S stages.

Interpretation Our proposed ICON-S staging system for HPV+ oropharyngeal cancer is suitable for the 8th edition of the Union for International Cancer Control/American Joint Committee on Cancer TNM classification. Future work is needed to ascertain whether T and N categories should be further refined and whether non-anatomical factors might augment the full classification.
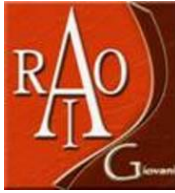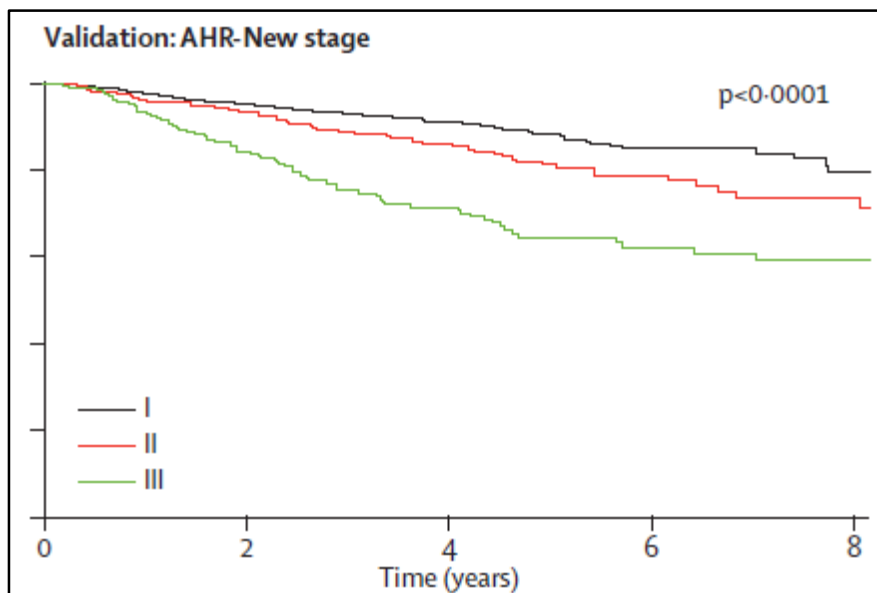
Si tratta di uno studio retrospettivo su circa 2000 pazienti affetti da tumori dell'orofaringe HPV-correlato trattati in grossi centri nord-americani ed europei. Gli autori riconoscono l'importanza di differenziare quanto prima i criteri stadiativi dei pazienti con tumori HPV-positivi da quelli HPV-negativi. Lo studio ICON-S rappresenta pertanto il primo sforzo internazionale adottando un disegno del tipo *"training-validation"* per proporre una nuova classificazione basata sul sistema TNM. Analogamente all'articolo soprariportato, il sistema classificativo attuale non si è dimostrato in grado di differenziare l'outcome dei pazienti in termini di OS ad eccezione di stadi di malattia estremamente avanzati (IVB):
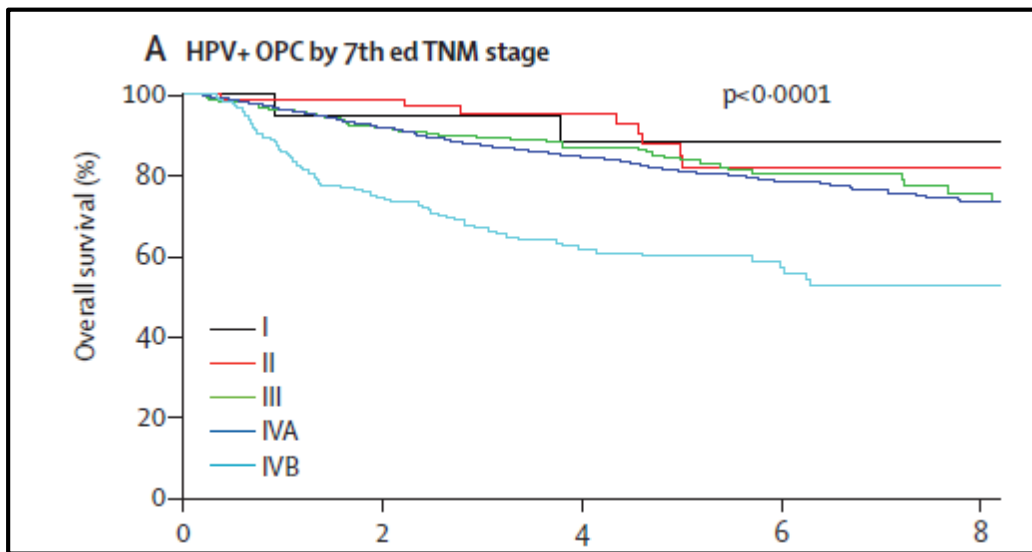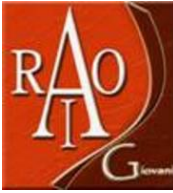

D'altro canto l'utilizzo di un Sistema di classificazione in cui i livelli linfonodali erano ridotti a sole 3 categorie (analogamente a quanto viene fatto nella stadiazione del rinofaringe) unitamente ad un'analisi sia di tipo RPA che, in maggiore misura, di tipo AHR (*adjusted-hazard ratio*) ha permesso di distinguere in maniera ottimale la prognosi dei pazienti:

I risultati ottenuti hanno pertanto portato gli Autori ha ideare un sistema classificativo (ICON-S) in 3 stadi, mantenendo una distinzione per i pazienti metastatici (stadio IV):

ICON-S stage classification	T1	T2	T3	T4
N0	I	I	II	III
N1	I	I	II	III
N2	II	II	II	III
N3	III	III	III	III

Conclusioni

Il modello classificativo descritto rappresenta ad oggi la miglior classificazione *evidence-based* possibile, formalizzando quanto già suggerito da altri studi (ad es. la riduzione del numero delle categorie N).