ABVD (8 cycles) versus BEACOPP (4 escalated cycles ≥4 baseline): final results in stage III–IV low-risk Hodgkin lymphoma (IPS 0–2) of the LYSa H34 randomized trial†


1Department of Onco-Hematology, Archet Hospital, Nice; 2Department of Hematology, Saint-Louis Hospital, Paris; 3Department of Hematology, Nancy Hospital; 4Department of Hematology, Henri Mondor Hospital, Creteil; 5Department of Hematology, Besancon Hospital; 6Department of Hematology, la Pitié-Salpétrière Hospital, Paris; 7Department of Hematology, CHU de Dijon Hospital, Dijon; 8Department of Hematology, St Etienne Hospital, St Etienne; 9Department of Hematology, Courantcy Cancer Institute, Reims; 10Department of Hematology, Reims Hospital, Reims; 11Department of Hematology, Corbeil Hospital, Corbeil Essonnes; 12Department of Hematology, Lyon Sud Hospital, Pierre Bente; 13Department of Hematology, Leon Berard Cancer Center, Lyon; 14Department of Hematology, St Antoine Hospital, Paris; 15Department of Hematology, Colmar Hospital, Colmar, France; 16Department of Hematology, Mont Godinne Hospital, Yvoir, Belgium; 17Department of Hematology, Gustave Roussy Institute, Villejuif, France

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Background: Treatment with escalated BEACOPP achieved a superior time to treatment failure over ABVD in patients with disseminated Hodgkin lymphoma. However, recent clinical trials have failed to confirm BEACOPP overall survival (OS) superiority over ABVD. In addition, the gain in low-risk patients is still a matter of debate.

Patients and methods: We randomly compared ABVD (8 cycles) with BEACOPP (escalated 4 cycles ≥baseline 4 cycles) in low-risk patients with an International Prognostic Score (IPS) of 0–2. The primary end point was event-free survival (EFS). This parallel group, open-label phase 3 trial was registered under #RECF0219 at French National Cancer Institute.

Results: One hundred and fifty patients were randomized in this trial (ABVD 80, BEACOPP 70): 28 years was the median age, 50% were male and IPS was 0–1 for 64%. Complete remission rate was 85% for ABVD and 90% for BEACOPP. Progression or relapses were more frequent in the ABVD patients than in the BEACOPP patients (17 versus 5 patients). With a median follow-up period of 5.5 years, seven patients died: six in the ABVD arm and one in the BEACOPP arm (HL 3 and 0, 2nd cancer 2 and 1, accident 1 and 0). The EFS at 5 years was estimated at 62% for ABVD versus 77%, for BEACOPP [hazards ratio (HR) = 0.6, P = 0.07]. The progression-free survival (PFS) at 5 years was 75% versus 93% (HR = 0.3, P = 0.007). The OS at 5 years was 92% versus 99% (HR = 0.18, P = 0.06).

Conclusion: Fewer progressions/relapses were observed with BEACOPP, demonstrating the high efficacy of the more intensive regimen, even in low-risk patients. However, additional considerations, balancing treatment-related toxicity and late morbidity due to salvage may help with decision-making with regard to treatment with ABVD or BEACOPP.

Key words: Hodgkin lymphoma, intensive chemotherapy, phase 3 trial, prognostic factors, secondary malignancy

*Correspondence to: Prof. Nicolas Mounier, Onco-Hématology Department, Archet Hospital, 151 route de Saint Antoine Ginestière, 06200 Nice, France. Tel: +33-4-92-03-58-41; E-mail: mounier.n@chu-nice.fr

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introduction

A majority of patients with Hodgkin lymphoma (HL) are now being cured, even in the advanced stages. However, balancing the risks and benefits, treatment strategies are still a matter of debate. The standard approach to treatment uses doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) as first-line therapy [1]. For the 25% of patients who relapse after initial treatment, second-line treatment with high-dose chemotherapy is followed by autologous stem cell transplantation. The alternative approach aims to cure as many patients as possible with aggressive first-line chemotherapy using increased doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (escalated BEACOPP) [2–4]. Accumulated data have shown better progression-free survival (PFS) and overall survival (OS) rates, but this alternative approach exposes patients to substantial acute chemotherapy-related toxicity [5, 6].

Clinical prognostic indices may help to identify patients at a low risk of treatment failure to be considered for standard treatment or to identify patients at a higher risk to be considered for more intensive therapy or a combination with new drugs. For more than 15 years, the International Prognostic Score (IPS), which incorporates seven clinical parameters, has been the most widely accepted risk stratification model [7]. However, for patients treated in the ABVD era, IPS predicts for a much narrower range of outcomes than has been previously noted [8]. More specifically, the difference in PFS in patients with low-risk and high-risk scores has diminished to 15%.

The intergroup trial 20012, led by EORTC, grouping LYSa (formerly GELA), ALLG, NCRI LYG, GELCAB, NCIC and NLLG was a phase 3 trial to assess whether treatment with four cycles of escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) followed by four cycles of BEACOPP-baseline improved event-free survival (EFS) when compared with the eight cycles of the standard ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) regimen in patients with measurable stage III or IV HL, with a high-risk IPS (≥3)[9]. We present herein the results of a trial conducted in parallel to the intergroup 20012 trial in LYSa centers only, which aimed to assess the EFS gain after stratification in low-risk patients with an IPS ranging from 0 to 2 (registered under #REC0219 at French National Cancer Institute).

methods

patients

Patients were included in the study if they had histologically documented HL (except lymphocyte predominant nodular type), were treatment naïve, were 16–60 years old, were a clinical stage III or IV, had at least one bi-dimensionally measurable target lesion (even if extranodal only), had a WHO performance status of 0–2, had an IPS of 0–2 and had an absence of other malignancies (except basal cell skin and in situ uterine cervix carcinomas). Patients were excluded from the study if they had an absence of measurable disease, were of childbearing-potential without the use of effective contraception, were pregnant or lactating, had an active infection, had severe cardiopulmonary, neurological or metabolic disease that interfered with normal life, or had inadequate liver (bilirubin ≤2.5×normal) or renal (creatinine ≤150 µmol/l or ≤2.0 mg/dl) function (unless the inadequate function was due to HL).

study design and treatment

This was a parallel group, open-label randomized trial. We used computer-assisted permuted-block randomization (block size of four, allocation ratio 1:1) to assign treatment. Randomization was stratified by participating center. A statistician located centrally at the GELA research clinic supervised the randomization procedure.

The doses and schedules of the chemotherapy combinations are listed in supplementary Table S1 available at Annals of Oncology online. ABVD was administered for eight cycles, depending on the response assessed at the end of cycles 4 (C4), 6 (C6) and 8 (C8), using clinical and computed tomography (CT) criteria. Positron emission tomography (PET) scans were not allowed. BEACOPP was administered for eight cycles (escalated for four cycles, then followed by baseline administration for four cycles). The checkpoints for pursuing the treatment as planned were: achievement at the end of the fourth cycle (i.e. the 22nd or 28th day, depending on the arm) of at least a partial response (regression of more than 50%, i.e. PR >50%) and normalization of bone marrow biopsy in the case of initial involvement; achievement at the end of C8 of at least a PR >75%. Patients in CR after four or six cycles have to complete the scheduled eight ABVD or BEACOPP cycles. Any protocol therapy discontinuation while the patient was in PR, progression, or unknown status or was administered a new treatment was defined and recorded as an event (treatment failure). No radiotherapy could be given as part of the protocol treatment unless it was considered as an event. The prophylactic administration of G-CSF and trimethoprim/sulfamethoxazole was mandatory in the BEACOPP arm. The evaluation of response was carried out according to the Response Evaluation Criteria for HL [10]. Local or national ethics committees approved the study protocol, according to the laws of every country. The study was done in accordance with the Declaration of Helsinki. Patients provided written informed consent before inclusion. Hematologic and non-hematologic toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (Version 2.0).

statistical analysis

The EFS was the primary end point, which was defined as the time from randomization to the early discontinuation of the protocol treatment, the absence of complete remission (CR/CRu) after eight cycles or the occurrence of relapse, progression or death. The study was designed for 150 patients to be randomized over 5 years. It was determined that 26 events were required to detect a 15% increase in the 5-year EFS rate from 75% (ABVD) to 90% (BEACOPP), based on a one-sided log-rank test at error rates of α = 0.05 and β = 0.20. Secondary end points were defined as CR/CRu, PFS, OS and the occurrence of second malignancies. We calculated hazard ratios (HR) by the Cox proportional-hazards analysis. Dose intensity for chemotherapy drugs was calculated according to Hrynuk and Goodyear [11]. We compared patients’ qualitative variables with the χ² or Fisher’s exact test. We judged differences significant if P-values were <0.05 (two-sided). All analyses were conducted as intention-to-treat using SAS 9.2 software.

results

As stated in the Methods section, 150 eligible patients were enrolled in the study between February 2003 and August 2008. Pathological characteristics were centrally reviewed in 148 patients (98%). Most of the patients (89%) had a nodular sclerosis subtype of HL. The median age of the patients was 28 years (range: 16–60). The sex ratio was 1:1. Eighty-seven patients (64%) presented with an IPS of 0–1. Seventy-two patients (48%) presented with stage IV disease and 30 (22%) presented with a tumor mass larger than 10 cm. Sixty-one patients (40%) had at
least one extranodal site. The marrow was involved in 12 patients (8%). Eighty patients were randomized to the ABVD arm and 70 were randomized to the BEACOPP arm. The demographic and baseline disease characteristics, according to treatment arm, are listed in Table 1.

### Table 1. Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ABVD (n = 80)</th>
<th>%</th>
<th>BEACOPP (n = 70)</th>
<th>%</th>
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<tbody>
<tr>
<td>Age (years)</td>
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<td></td>
<td></td>
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<tr>
<td>Median</td>
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<td>28</td>
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<td>Range</td>
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<td>16–58</td>
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<td>&lt;45</td>
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<td>Female</td>
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<td>48</td>
<td>37</td>
<td>53</td>
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<tr>
<td>Erythrosite sedimentation rate</td>
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<td>40</td>
<td>62</td>
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<td>57</td>
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<td>Bone marrow involvement</td>
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</tr>
<tr>
<td>International prognostic index</td>
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<td>17</td>
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<td>6</td>
</tr>
<tr>
<td>Missing</td>
<td>9</td>
<td>5</td>
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</tbody>
</table>

### response to treatment

As shown in Figure 1, treatment started in 77 patients and 68 because three withdrew their consent and two presented staging errors. Overall, 68 out of 77 completed the ABVD treatment and 61 out of 68 completed BEACOPP. No deaths occurred due to toxicity.

The main reasons for treatment discontinuation were treatment failure (3 and 2), patient refusal (3 and 2) and toxicity (1 and 3). In the ABVD arm, the toxicity occurred as one case of intracardiac thrombosis. In the BEACOPP arm, there were two infectious complications (colitis, pneumopathy) and one allergy to etoposide.

At the end of the treatments, failure to achieve CR occurred in 15 patients: 10 in the ABVD arm and 5 in the BEACOPP arm. As shown in Table 2, the CR rate was 85% for ABVD and 90% for BEACOPP. After the end of treatment evaluation, three non-CR patients were given consolidation radiotherapy in ABVD (protocol violation) and none in BEACOPP.

### survival outcomes

The median follow-up period was 5.5 years. Seventeen relapses were observed: 14 patients in the ABVD arm versus 3 in the BEACOPP arm. The EFS at 5 years was estimated at 62% (50; 71) versus 77% (65; 85), respectively [HR = 0.6 (0.33; 1.06), \( P = 0.07 \)] (Figure 2). Regarding the sample size computation hypothesis on the primary end point, the one-sided log-rank test \( P \)-value for EFS was estimated at 0.038. The PFS at 5 years was 75% (63; 83) versus 93% (83; 97) [HR = 0.3 (0.12; 0.77), \( P = 0.007 \)] (Figure 3). Among the 22 patients who failed to respond or who relapsed, 12 patients among the 17 patients in the ABVD arm and 5 patients among the 5 patients in the BEACOPP arm received stem cell transplantation after a salvage regimen.

Overall, seven patients died: six in the ABVD arm and one in the BEACOPP arm. In the ABVD arm, the cause of death was the HL for three patients, second cancer for two patients and...
accident for the remaining patient. The only death in the BEACOPP arm was due to a second malignancy. The 5-year OS was estimated at 92% (81; 97) versus 99% (90; 100) [HR = 0.18 (0.02; 1.53), \( P = 0.06 \)].

adverse events
A total of 1124 cycles of chemotherapy were administered with 597 administered ABVD and 527 administered BEACOPP. Hospitalizations occurred in 11% (ABVD) and 37% (BEACOPP) of the patients. The main reason for hospitalization was the administration of chemotherapy (81% of cases). The other reasons for hospitalization were the management of toxicity (8%) and tumor symptoms (5%). The median dose intensity was 98%, 92%, 97% and 98% for doxorubicin, bleomycin, vinblastine and dacarbazine in the ABVD arm. It was 100%, 95%, 98%, 100%, 100% and 99% for doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide and procarbazine in the escalated BEACOPP arm and 98%, 90%, 80%, 98%, 99% and 96%, respectively, in the baseline BEACOPP arm. There were 20 severe adverse events in the ABVD arm versus 62 in the BEACOPP arm; all were in relation with treatment-related morbidity. Grade 3–4 hematological events were reported during treatment in the ABVD and BEACOPP arms in 8% and 35% of the patients for febrile neutropenia, 42% and 75% of the patients for granulocytes and 0% and 21% of the patients for platelets. The most frequently reported grade 3 or 4 non-hematological events in the ABVD and BEACOPP arms were fatigue (2% and 7%) and sensitive neuropathy (0% and 7%). Other grade 3 or 4 adverse events were not clinically relevant in both arms (Table 3).

Second cancers occurred in five ABVD patients and in one BEACOPP patient (non-HL 2 and 1, lung 1 and 0, digestive 2 and 0). The three lymphoma subtypes were: T-not otherwise specified and T-angioimmunoblastic for the ABVD cases and EBV-induced B large cell lymphoma for the BEACOPP case. The three patients died from their lymphomas. Among the five ABVD patients, three received second-line HL treatment. The T-Angioimmunoblastic lymphoma case occurred after DHAP, and two solid tumors occurred after ASCT following ICE or DHAP. See supplementary Figure S1 available at Annals of Oncology online.

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**Table 2.** Response after treatment

<table>
<thead>
<tr>
<th></th>
<th>ABVD ((n = 77))</th>
<th>BEACOPP ((n = 68))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response after 8 cycles</td>
<td>( n = 68 ) %</td>
<td>( n = 61 ) %</td>
</tr>
<tr>
<td>Complete response</td>
<td>34</td>
<td>50</td>
</tr>
<tr>
<td>Unconfirmed complete response</td>
<td>24</td>
<td>35</td>
</tr>
<tr>
<td>Partial response</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Stable disease</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Stop before 8 cycles</td>
<td>( n = 9 )</td>
<td>( n = 7 )</td>
</tr>
</tbody>
</table>

**discussion**
A homogeneous group of patients with good prognoses with stage III and IV HL were enrolled in the present phase III randomized trial to assess the range of benefit achieved in increasing the chemotherapy dose intensity in the conventional range. No radiotherapy was allowed in this trial. ABVD \( \times 8 \) cycles was selected as the standard regimen and BEACOPP\(_{\text{escalated}} \times 4 \) ≥ BEACOPP\(_{\text{baseline}} \times 4 \) was selected as the experimental arm. The difference in outcomes was favorable in the experimental arm. The 5-year PFS was significantly improved in the experimental arm. There were 20 severe adverse events in the ABVD arm versus 62 in the BEACOPP arm; all were in relation with treatment-related morbidity. Grade 3–4 hematological events were reported during treatment in the ABVD and BEACOPP arms in 8% and 35% of the patients for febrile neutropenia, 42% and 75% of the patients for granulocytes and 0% and 21% of the patients for platelets. The most frequently reported grade 3 or 4 non-hematological events in the ABVD and BEACOPP arms were fatigue (2% and 7%) and sensitive neuropathy (0% and 7%). Other grade 3 or 4 adverse events were not clinically relevant in both arms (Table 3).

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**Figure 2.** Event-free survival according to treatment arm \( P = 0.07 \).
arm (75% for ABVD versus 93% for BEACOPP, \( P = 0.008 \)). However, the significance level was not reached for our primary end point (5-year EFS 62% for ABVD versus 77% for BEACOPP, \( P = 0.07 \)) or for the 5-year OS (92% for ABVD versus 99% for BEACOPP, \( P = 0.08 \)).

Good results with ABVD treatment have also been published by Moccia et al. [8]. In an analysis restricted to patients <65 years old, results from Moccia et al. showed a 5-year OS ranging from 92% for patients with 2 IPS factors to 98% for patients with no adverse factors and showed a PFS ranging from 80% to 88%, respectively. In the present trial comparing BEACOPP with ABVD, treatment was administered full dose with an excellent compliance; the lack of significant gain could be explained by the small sample size of the study population (\( n = 150 \)). Therefore, although the PFS results revealed the long-awaited dose–response effect, it appears that BEACOPP would be a PFS benefit to 5–7% of the patients if used initially instead of ABVD. This finding has also been suggested by the two other studies that randomized ABVD and escalated-BEACOPP in patients with advanced HL [12, 13]. The baseline IPS (<3 versus \( \geq 3 \)) did not significantly influence the outcome of treatment in a study conducted by Viviani et al., and the gain in 5-year PFS was not significant (75% for ABVD versus 90% for BEACOPP, \( P = 0.125 \)) in a study conducted by Federico et al.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{(A) Progression-free survival according to treatment arm \( P = 0.007 \). (B) Overall survival according to treatment arm \( P = 0.06 \).}
\end{figure}
The immediate morbidity during treatment was higher in the BEACOPP arm: 8% of patients experienced febrile neutropenia in the ABVD arm versus 35% in the BEACOPP arm. However, all of the complications were manageable with growth factor support and a strict dose reduction, even in our multicenter setting, and no deaths occurred due to toxicity [14]. With a median follow-up period of 5.5 years, late morbidity could not be assessed. Thus far, no difference has emerged concerning the second solid tumors. Second cancers occurred in cardiac and pulmonary functions. However, a striking point was noted concerning the second solid tumors. Second cancers occurred in five ABVD patients and in one BEACOPP patient (NHL 2 and 1, lung 1 and 0, other 2 and 0). Among the five ABVD patients, three received second-line HL treatment. These findings suggested that HL relapse after ABVD could now be cured but at the price of complications such as secondary cancers.

At the present time, physicians are not able to predetermine which patients can be cured by ABVD and which patients will benefit from escalated BEACOPP. An interim fluorodeoxyglucose PET assessment—i.e., after two cycles of chemotherapy—can be used to predict a final outcome in HL [15, 16]. These promising findings lead investigators to launch several ongoing trials to test PET-based strategies in advanced disease. Another aim is to improve the prediction of a final outcome using molecular profiling. Recently, Scott et al. [17] succeeded in developing a predictor of survival using gene expression measured in a formalin-fixed paraffin-embedded biopsy. There was a 29% absolute difference in the 5-year OS between the high- and low-risk groups, independent of the IPS. As the study population did not receive BEACOPP, further studies are required to determine whether the high risk of death identified by the model can be overcome by BEACOPP or by novel agents combined with ABVD. In a recent trial, Younes et al. [18] treated 51 patients with six cycles of 0.6–1.2 mg/kg of brentuximab vedotin plus ABVD (BV–ABVD) or 1.2 mg/kg of brentuximab vedotin with AVD (BV–AVD). Notably, 11 of the 25 (44%) patients treated with BV–ABVD experienced pulmonary toxicity resulting in two deaths compared with 0% in

the BV–AVD group. At the end of treatment, the CR was estimated at 95% for the patients treated with BV–ABVD and 96% for BV–AVD.

### conclusion

As PET and molecular study results are not yet available, treatment with BEACOPP should be a robust option over ABVD because, even in low-risk patients, it significantly improves PFS. However, considering the high burden, morbidity and costs related to BEACOPP, the results of this study raise the issue of identifying these patients early to be able to offer them an alternative treatment on the ABVD platform.

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### disclosure

The authors have declared no conflicts of interest.

### references

Background: Head and neck squamous cell carcinoma refers to a heterogeneous disease frequently aggressive in its biologic behavior. Despite the improvements in the therapeutic modalities, the long-term survival rate remained unchanged over the past decade and patients with this type of cancer are at a high risk of developing recurrence. For this reason, there is a great need to find better ways to foresee outcome, to improve treatment choices, and to enable a more personalized approach.

Patients and methods: Nine microarray gene expression datasets, reporting survival data of a total of 841 samples, were retrieved from publicly repositories. Three datasets, profiled on the same version of microarray chips, were selected and merged following a meta-analysis approach to build a training set. The remaining six studies were used as independent validation sets.

Results: The training set led us to identify a 172-gene signature able to stratify patients in low or high risk of relapse [log-rank, \( P = 2.44e-05; \) hazard ratio (HR) = 2.44, 95% confidence interval (CI) 1.58–3.76]. The model based on the 172 genes was validated on the six independent datasets. The performance of the model was challenged against other proposed prognostic signatures (radiosensitivity index, 13-gene oral squamous cell carcinoma signature, hypoxia metagene, 42-gene high-risk


Comprehensive gene expression meta-analysis of head and neck squamous cell carcinoma microarray data defines a robust survival predictor

L. De Cecco1, P. Bossi2, L. Locati2, S. Canevari1,3* & L. Licitra2

1Functional Genomics and Informatics, Department of Experimental Oncology and Molecular Medicine; 2Head and Neck Medical Oncology Unit, Department of Molecular Oncology; 3Molecular Therapies, Department of Experimental Oncology and Molecular Medicines, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

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Background: Head and neck squamous cell carcinoma refers to a heterogeneous disease frequently aggressive in its biologic behavior. Despite the improvements in the therapeutic modalities, the long-term survival rate remained unchanged over the past decade and patients with this type of cancer are at a high risk of developing recurrence. For this reason, there is a great need to find better ways to foresee outcome, to improve treatment choices, and to enable a more personalized approach.

Patients and methods: Nine microarray gene expression datasets, reporting survival data of a total of 841 samples, were retrieved from publicly repositories. Three datasets, profiled on the same version of microarray chips, were selected and merged following a meta-analysis approach to build a training set. The remaining six studies were used as independent validation sets.

Results: The training set led us to identify a 172-gene signature able to stratify patients in low or high risk of relapse [log-rank, \( P = 2.44e-05; \) hazard ratio (HR) = 2.44, 95% confidence interval (CI) 1.58–3.76]. The model based on the 172 genes was validated on the six independent datasets. The performance of the model was challenged against other proposed prognostic signatures (radiosensitivity index, 13-gene oral squamous cell carcinoma signature, hypoxia metagene, 42-gene high-risk