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CLINICAL AND PATHOLOGICAL PROGNOSTIC FACTORS IN PATIENTS WITH STAGE III–IVA-B ORAL SQUAMOUS CELL CARCINOMA

*O.V. Kravets[1,] *, V.S. Protsyk[1], O.V. Burtyn[1], O.V. Hlynin[1], V.H. Hurianov[2]*
[1]*National Cancer Institute, Kyiv 03022, Ukraine*
[2]*Bogomolets National Medical University, Kyiv 01601, Ukraine*

The *aim* of the work was to study clinical and pathological factors affecting the prognosis of the disease in patients with stage III–IVA-B oral squamous cell carcinoma (OSCC). *Materials and Methods:* A retrospective review of medical records of 234 patients with stage III–IVA-B OSCC was performed in order to study the impact of clinical and pathological factors on disease-free survival (DFS) and overall survival (OS). *Results:* Multivariable analysis of clinical factors revealed a statistically significant effect of stage IVA-B and the presence of surgical complications on DFS (hazard ratio (HR) = 4.9 (95% confidence interval (CI) 2.9–8.3), $p < 0.001$; HR = 1.6 (95% CI 1.0–2.6), $p = 0.047$), respectively. Stage IVA-B, the presence of surgical complications and the retromolar trigone subsite were found to have a statistically significant impact on OS (HR = 4.0 (95% CI 2.5–6.5), $p < 0.001$; HR = 1.8 (95% CI 1.1–2.8), $p = 0.01$; HR = 1.9 (95% CI 1.1–3.2), $p = 0.02$), respectively. Multivariable analysis of pathological factors showed a statistically significant effect of positive resection margins, the multiple lymph node involvement and high-grade tumor on DFS (HR = 3.7 (95% CI 2.0–6.6), $p < 0.001$; HR = 4.3 (95% CI 2.8–6.7), $p < 0.001$; HR = 1.6 (95% CI 1.1–2.2), $p = 0.01$), respectively. Besides, positive resection margins and multiple lymph node involvement were found to cause a statistically significant impact on the OS (HR = 3.6 (95% CI 2.0–6.5), $p < 0.001$; HR = 3.7 (95% CI 2 5–5.6), $p < 0.001$), respectively. A tumor grade tended to worsen OS (HR = 1.4 (95% CI 1.0–1.9), $p = 0.053$). *Conclusion:* Stage IVA, B, the presence of surgical complications, the retromolar trigone subsite, positive resection margins, multiple lymph node involvements and high-grade tumor were found to be significant clinical and pathological prognostic factors in patients with stage III–IVA-B OSCC.
***Key Words*: oral squamous cell carcinoma, clinical and pathological prognostic factors.**

According to the National Cancer Registry of Ukraine, the incidence of oral cancer is 6.1 per 100,000 population. At the time of diagnosis in 2017, 50.8% of patients were found to have stages III–IV, and the one-year mortality incidence was 38.8% [1]. Despite significant advances in the diagnosis and treatment of oral squamous cell carcinoma (OSCC) patients, the overall 5-year survival rate in most countries of the world does not exceed 45–50% and has remained unchanged over the past decades [2].

Treatment of patients with stage III–IVA-B OSCC includes surgical interventions followed by radiotherapy or simultaneous chemoradiation therapy [3]. Clinical and pathological prognostic factors are considered when planning the strategy of adjuvant treatment and determining the prognosis of the disease. Current investigations are being focused on finding independent risk factors or a group of factors that have prognostic significance in OSCC patients. Better understanding of the factors involved in the disease progression can prove to be beneficial for deciding on the most optimal postoperative therapy and improved patient survival [4–6].

In spite of the fact that recent studies have concentrated mainly on new molecular markers, the role of clinical and pathological factors remains crucial when planning adjuvant therapy in OSCC patients [7]. However, so far, little research has been conducted to study clinical and pathological prognostic factors exclusively in patients with stage III–IVA-B OSCC, not in patients with head and neck cancer in general. In addition, some factors are still controversial, understudied and researchers have reported contradictory results [8–10]. The aim of the work was to study the effect of clinical and pathological factors on the prognosis of the disease in patients with stage III–IVA-B OSCC.

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*Correspondence: E-mail: kravetso.doc@ukr.net
Abbreviations used: CI – confidence interval; DFS – disease-free survival; HR – hazard ratio; OS – overall survival; OSCC – oral squamous cell carcinoma; TNM – International System of Classification of Tumors, based on tumor-node-metastasis.

MATERIALS AND METHODS

A retrospective review of the medical records of 234 OSCC patients, who were treated in the Head and Neck Department of the National Cancer Institute from 2008 to 2013, was performed. The study included stage III–IVA-B OSCC patients, who underwent surgical treatment followed by radiotherapy or chemoradiation therapy. Exclusion criteria from the study were as follows: immunotherapy, chemotherapy or radiation therapy prior to surgical treatment; distant metastases; tumor recurrence after previous treatment. The study was approved by the Ethic Committee of the National Cancer Institute.

Tumors were staged according to the International Union against Cancer (UICC) 2002 tumor, node, metastasis (TNM) classification.

The impact of clinical and pathological factors on disease-free survival (DFS) and overall survival (OS) was studied. There were assessed clinical prognostic factors, including gender, age, oral cavity subsite, clinical tumor stage, pathologic stage, and the presence of surgical complications. The evaluated pathological factors were as follows: positive surgical margins, extracapsular nodal extension, multiple lymph node

involvement, perineural invasion, lymphovascular invasion, tumor thickness, and histopathological grade.

Statistical analyses were performed with MedCalc v.18.10 (MedCalc Software Inc, Broekstraat, Belgium, 1993–2018).

Kaplan — Meier method was used to analyze survival characteristics. Hazard ratios (HRs) with 95% confidence intervals (95% CI) for OS and DFS were calculated. The Cox proportional hazards regression model was used for the assessment of the effect of several risk factors on survival (for adjusted HRs calculation). To select independent variables of the multivariable models, there was employed a stepwise method. The significance threshold was set at $p < 0.05$.

RESULTS

The research is based on the study of clinical and pathological prognostic factors in 234 patients with stages III–IVA-B OSCC. Of these, 209 (89.3%) were male and 25 (10.7%) were female. The average age of patients was 55.9 ± 9.1 years. The sites where cancer was diagnosed included: oral tongue (n = 114, 48.7%), floor of mouth (n = 59, 25.5%), buccal mucosa (n = 28, 12%), lower alveolar ridge (n = 16, 6.8%), retromolal trigone (n = 12, 5.1%), and upper alveolar ridge/hard palate (n = 5, 2.1%). The extent of the malignant disease spread by the TNM classification corresponded to T2–4N0–3M0: 103 (44.0%) patients had stage III, 130 (55.6%) patients had stage IVA and 1 (0.4%) patient had stage IVB. The distribution by T-category was as follows: T3 was found in 141 (60.3%) patients, 76 (32.5%) patients had T4, and 17 (7.3%) patients had T2. By N-category, the patients were distributed as follows: 89 (38.0%) patients were diagnosed with N2, 80 (34.2%) — with N0, 64 (27.4%) with N1, and one patient (0.4%) had N3.

All patients underwent surgery for plastic reconstruction of postoperative defects with free or regional flaps. Surgical complications were diagnosed in 47 (20.1%) patients. If factors of high risk of recurrence (positive resection margins or extracapsular nodal extension) were verified histologically, adjuvant chemoradiotherapy was performed. Patients having intermediate risk factors (multiple lymph node involvement, perineural invasion, lymphovascular invasion, primary tumor of pT3/4, high-grade tumor) received adjuvant radiation therapy. Chemoradiation therapy was administered to 77 (32.9%) patients; 157 (67.1%) patients underwent radiation therapy. The overall five-year survival was 55.4%, and the five-year DFS was 59.6%.

When analyzing pathological prognostic factors, we obtained the following data: positive resection margins were found in 15 (6.5%) patients; extracapsular nodal extension was detected in 64 (27.3%) patients; multiple lymph node involvement was revealed in 89 (38.0%) patients; 121 (51.7%) patients had perineural invasion; lymphovascular invasion was identified in 150 (64.1%) patients. Seventy-two (30.7%) patients had 6–10 mm thick tumors; in 116 (49.6%), they were 11–20 mm thick; tumor thickness of >20 mm was in 46 (19.7%) patients. Sixty-two (26.5%) patients were diagnosed with G1 tumor grade; 145 (62.0%) patients had G2; G3 tumor grade was found in 27 (11.5%) patients.

Analysis of the prognostic impact of clinical factors on the DFS. Univariable analysis revealed the association of DFS with the clinical extent of the primary tumor spread ($p < 0.001$), patients with greater T were at *higher* risks for recurrences, HR = 2.0 (95% CI 1.4–2.9) for each grade of an increase in value. Moreover, the association between the stage of the process and DFS ($p < 0.001$) was found, patients with a *higher stage* of the disease were at *higher* risks for recurrences, HR = 4.8 (95% CI 2.8–8.1). There was no relationship between DFS and gender, age, the site of the tumor or the presence of surgical complications.

To select independent variables of the multivariable models, there was used a stepwise method (a variable was entered into the model if $p < 0.1$, a variable was removed from the model if $p > 0.2$). A multivariable model confirmed the relationship between the stage of the process and DFS ($p < 0.001$); stage IVA-B was associated with *higher* risks for recurrences, HR = 4.9 (95% CI 2.9–8.3), as compared with stage III (when standardized by the presence of surgical complications and the site of the process). Besides, patients having surgical complications were found to be at higher risk of recurrences, when standardized by the stage of the process ($p = 0.047$), HR = 1.6 (95% CI 1.0–2.6).

Analysis of the prognostic impact of clinical factors on OS. Univariable analysis showed the association of OS with the clinical extent of the tumor spread ($p < 0.001$), patients with greater T had worse OS, HR = 1.9 (95% CI 1.3–2.7) for each grade an increase in value. There was also seen the relationship between the stage of the process and OS ($p < 0.001$), patients with stage IVA-B were at higher risks, HR = 3.8 (95% CI 2.4–6.1). No association of OS with gender, age, the site of the tumor or presence of surgical complications was found.

To select independent variables of the multivariable models, there was used a stepwise method (a variable was entered into the model if $p < 0.1$, a variable was removed from the model if $p > 0.2$). A multivariable model confirmed the relationship between OS and the stage of the process ($p < 0.001$), patients with stage IVA-B had worse OS, HR = 4.0 (95% CI 2.5–6.5), as compared with stage III (when standardized by the presence of surgical complications and the location of the process). In addition, there was revealed the higher risk of recurrence in the presence of surgical complications when standardized by the stage and site of the process ($p = 0.01$), HR = 1.8 (95% CI 1.1–2.8). Besides, the association ($p = 0.02$) of the tumor site with OS was found when standardized by the stage and the presence of surgical complications. Patients with the tumor in the retromolal trigone had worse OS, HR = 1.9 (95% CI 1.1–3.2), as compared with other sites. The results are presented in Tables 1, 2.

Analysis of the prognostic impact of pathological factors on DFS. Univariable analysis revealed the association between DFS and all pathological factors studied, including positive resection margins,

extracapsular nodal extension, multiple lymph node involvement, perineural invasion, lymph vascular invasion, tumor thickness, and tumor grade.

To select independent variables of the multivariable models, there was used a stepwise method (a variable was entered into the model if $p < 0.1$, a variable was removed from the model if $p > 0.2$). A multivariable model showed the relationship between DFS and positive resection margins ($p < 0.001$), patients with positive resection margins were at higher risks of recurrence, HR = 3.7 (95% CI 2.0–6.6), when standardized by other risk factors. Patients with metastatic multiple lymph node involvement were found to have higher risks of recurrence ($p < 0.001$), HR = 4.3 (95% CI 2.8–6.7) when standardized by other risk factors. There were revealed higher risks of recurrence ($p = 0.01$) with an increase in the tumor grade, HR = 1.6 (95% CI 1.1–2.2) for each grade, when standardized by other risk factors.

Analysis of the prognostic impact of pathological factors on OS. Univariable analysis found a link between OS and all pathological factors studied, including positive resection margins, extracapsular nodal extension, multiple lymph node involvement, perineural invasion, lymphovascular invasion, tumor thickness and tumor grade.

To select independent variables of the multivariable models, there was used a stepwise method (a variable was entered into the model if $p < 0.1$, a variable was removed from the model if $p > 0.2$). A multivariable model revealed the relationship between OS and positive resection margins ($p < 0.001$), patients with positive resection margins had worse OS, HR = 3.6 (95% CI 2.0–6.5), when standardized by other risk factors. The risk increased ($p < 0.001$) in multiple lymph node involvement, HR = 3.7 (95% CI 2.5–5.6) when standardized by other risk factors. A higher tumor grade tended to worsen OS ($p = 0.053$) with an increase in the value, HR = 1.4 (95% CI 1.0–1.9), for each grade when standardized by other risk factors. The results are presented in Tables 3, 4.

DISCUSSION

The evaluation of clinical and pathological prognostic factors is essential when planning a strategy for adjuvant treatment and defining the prognosis of the disease. Based on our findings, such clinical factors as gender, age, and clinical extent of the primary tumor were not significant for the disease prognosis. While performing the multivariable analysis, such clinical factors as stage IVA, B, location of the tumor in the retromolar trigone and the presence of surgical complications were found to have the prognostic significance. A number of studies reported the value of prognostic significance of the stage of the disease and location of the tumor in the retromolar trigone, whereas the effect of surgical complications on the prog-

Table 1. Univariable model of the clinical factors impact on DFS and OS

Risk factor		DFS			OS		
		*Coefficient, b ± m	*p*-level	HR (95% CI)	*Coefficient, b ± m	*p*-level	HR (95% CI)
Gender		–0.02 ± 0.33	0.94	–	0.08 ± 0.31	0.79	–
Age		–0.003 ± 0,011	0.81	–	0.014 ± 0.011	0.18	–
Oral cavity subsite	"upper alveolar ridge/hard palate" *vs* "oral tongue"	–0.77 ± 1.01	0.45	–0.89 ± 1.01	–0.89 ± 1.01	0.38	–
	"floor of mouth" *vs* "oral tongue"	–0.01 ± 0.26	0.97	–0.01 ± 0.25	–0.01 ± 0.25	0.97	–
	"lower alveolar ridge" *vs* "oral tongue"	0.34 ± 0.38	0.38	0.36 ± 0.36	0.36 ± 0.36	0.32	–
	"retromolar trigone" *vs* "oral tongue"	0.36 ± 0.44	0.41	0.62 ± 0.38	0.62 ± 0.38	0.11	–
	"buccal mucosa" *vs* "oral tongue"	0.02 ± 0.34	0.94	0.01 ± 0.32	0.01 ± 0.32	0.99	–
Clinical tumor stage		0.71 ± 0.19	< 0.001	2.0 (1.4–2.9)	0.65 ± 0.18	< 0.001	1.9 (1.3–2.7)
Pathologic stage		1.56 ± 0.27	< 0.001	4.8 (2.8–8.1)	1.34 ± 0.24	< 0.001	3.8 (2.4–6.1)
Presence of surgical complications		0.36 ± 0.24	0.14	–	0.40 ± 0.23	0.09	–

Note: *Coefficients of univariable Cox regression models (b) and standard error (± m) are presented.

Table 2. Multivariable model of the clinical factors impact on DFS and OS

Risk factor	DFS			OS		
	*Coefficient, b ± m	*p*-level	HR (95% CI)	*Coefficient, b ± m	*p*-level	HR (95% CI)
Stage	1.59 ± 0.27	< 0.001	4.9 (2.9–8.3)	1.40 ± 0.24	< 0.001	4.0 (2.5–6.5)
Presence of surgical complications	0.49 ± 0.24	0.047	1.6 (1.0–2.6)	0.59 ± 0.23	0.01	1.8 (1.1–2.8)
Subsite: "retromolar trigone" *vs* "the others"	–	–	–	0.62 ± 0.27	0.02	1.9 (1.1–3.2)

Note: *Coefficients of multivariable Cox regression model (b) and standard error (± m) are presented.

Table 3. Univariable model of the pathological factors impact on DFS and OS

Risk factor	DFS			OS		
	*Coefficient, b ± m	*p*-level	HR (95% CI)	*Coefficient, b ± m	*p*-level	HR (95% CI)
Positive surgical margins	1.38 ± 0.30	< 0.001	4.0 (2.2–7.2)	1.30 ± 0.30	< 0.001	3.7 (2.0–6.6)
Extracapsular nodal extension	0.94 ± 0.22	< 0.001	2.6 (1.6–4.0)	1.03 ± 0.22	< 0.001	2.8 (1.8–4.3)
Multiple lymph node involvement	1.56 ± 0.22	< 0.001	4.7 (3.1–7.3)	1.38 ± 0.20	< 0.001	4.0 (2.7–6.0)
Perineural invasion	0.73 ± 0.22	0.001	2.1 (1.4–3.2)	0.60 ± 0.20	0.003	1.8 (1.2–2.7)
Lymphovascular invasion	0.95 ± 0.26	< 0.001	2.6 (1.6–4.3)	0.74 ± 0.23	0.001	2.1 (1.3–3.3)
Tumor thickness	0.42 ± 0.15	0.005	1.5 (1.1–2.0)	0.38 ± 0.14	0.007	1.5 (1.1–1.9)
Histopathological grade	0.65 ± 0.17	< 0.001	1.9 (1.4–2.7)	0.53 ± 0.16	0.001	1.7 (1.2–2.3)

Note: *Coefficients of univariable Cox regression models (b) and standard error (± m) are presented.

Table 4. Multivariable model of pathological factors impact on DFS and OS

Risk factor	DFS			OS		
	*Coefficient, b ± m	*p*-level	HR (95% CI)	*Coefficient, b ± m	*p*-level	HR (95% CI)
Positive surgical margins	1.30 ± 0.30	< 0.001	3.7 (2.0–6.6)	1.27 ± 0.30	< 0.001	3.6 (2.0–6.5)
Multiple lymph node involvement	1.46 ± 0.22	< 0.001	4.3 (2.8–6.7)	1.32 ± 0.21	< 0.001	3.7 (2.5–5.6)
Histopathological grade	0.44 ± 0.18	0.01	1.6 (1.1–2.2)	0.32 ± 0.17	0.053	1.4 (1.0–1.9)

Note: *Coefficients of multivariable Cox regression models (b) and standard error (± m) are presented.

nosis of the disease remains poorly understood [2, 11]. There is only one study that revealed association between the occurrences of relapse and the presence of surgical complications in OSCC patients [12]. Such an association has been unclear so far. The mechanism responsible for this association is thought to relate to the release of an inflammatory mediator, which interacts with residual tumor cells both locally and in the distant metastatic deposits. These can propagate tumor growth [13]. However, further research is needed to confirm this theory.

The choice of adjuvant therapy after surgical treatment of stage III–IVA-B OSCC patients is based on the evaluation of pathological prognostic factors. Positive resection margins and extracapsular nodal extension are considered as prognostic factors of high risk of relapse. Adjuvant therapy in patients with high-risk factors includes simultaneous combination of radiation and chemotherapy. Multiple lymph node involvement, lymphovascular invasion, perineural invasion, postoperative T3/4, high grade tumor, and level IV/V lymph node involvement are factors of intermediate risk of recurrence. Such patients undergo only adjuvant radiation therapy [7, 14]. Despite the fact that the statistically significant negative effects of intermediate risk factors have been confirmed in many studies, only the positive resection margins and extracapsular nodal tumor extension remain independent factors [8, 9, 14–17].

The multivariable analysis in our study confirmed the independent prognostic value of positive resection margins. It is noteworthy that no statistically significant effect of extracapsular nodal tumor extension on DFS and OS was revealed while conducting the multivariable analysis. Liu *et al.* obtained similar results [9]. Obviously, this was due to the fact that patients with extracapsular nodal tumor extension received adjuvant chemotherapy. Furthermore, our study found the independent prognostic significance of such pathological factors as high-grade tumor and multiple lymph node involvement. There was shown that high-grade tumors had a statistically significant impact on DFS (HR = 1.6 (95% CI 1.1–2.2), $p = 0.01$) and tended to worsen OS (HR = 1.4 (95% CI 1.0–1.9), $p = 0.053$). We also found a statistically significant effect of multiple lymph node involvement on DFS (HR = 4.3 (95% CI 2.8–6.7), $p < 0.001$) and OS (HR = 3.7 (95% CI 2.5–5.6), $p < 0.001$).

Thus, given the statistically significant negative impact of multiple lymph node involvement on DFS and OS and high-grade tumor on DFS, we are of the opinion that further studies are needed to establish whether adjuvant chemotherapy is advisable in patients with these pathological factors.

CONCLUSIONS

To summarize, stage IVA-B, the presence of surgical complications and location of the disease in the retromolar trigone were prognostically significant clinical factors in patients with stage III–IVA-B OSCC, who underwent surgical treatment with subsequent radiotherapy or chemoradiation therapy. Positive resection margins, multiple lymph node involvement and high-grade tumor were found to be pathological factors having prognostic significance. Further research is needed to study the advisability of adjuvant chemoradiotherapy in patients with multiple lymph node involvement and high-grade tumors.

REFERENCES

1. Cancer in Ukraine, 2016–2017. Incidence, mortality, indicators of the oncological service. Bull Nat Cancer Reg of Ukraine 2018; (19): 136.

2. Majumdar B, Patil S, Sarode SC, *et al.* Clinico-pathological prognosticators in oral squamous cell carcinoma: an update. Translat Res in Oral Oncol 2017; **2**: 1–14.

3. D'Cruz AK, Vaish R, Dhar H. Oral cancer: Current status. Oral Oncol 2018; **87**: 64–9.

4. Vincent N, Dassonville O, Chamorey E, *et al.* Clinical an histological prognostic factors in locally advanced oral cavity cancers treated with primary surgery. Eur Ann Otorhinolaryngol, Head Neck Dis 2012; **129**: 291–6.

5. Noble AR, Greskovich JF, Han J, *et al.* Risk factors associated with disease recurrence in patients with stage III/IV squamous cell carcinoma of the oral cavity treated with surgery and postoperative radiotherapy. Anticancer Res 2016; **36**: 785–92.

6. Mucoyama N, Suzuki H, Hanai N, *et al.* Pathological tumor volume predicts survival outcomes in oral squamous cell carcinoma. Oncol Lett 2018; **16**: 2471–7.

7. Colevas AD, Yom SS, Pfister DG, *et al.* NCCN Guidelines Insights: Head and Neck Cancers, Version 1.2018. J Natl Compr Canc Netw 2018; **16**: 479–90.

8. Matsushita Y, Yanamoto S, Takahashi H, *et al.* A clinicopathological study of perineural invasion and vascular invasion in oral tongue squamous cell carcinoma. Int J Oral Maxillofac Surg 2015; **44**: 543–8.

9. Liu SA, Wang CC, Jiang RS, *et al.* Pathological features and their prognostic impacts on oral cavity cancer patients among different subsites — A singe institutes experience in Taiwan. Scient Rep 2017; **7**: 7451.

10. Cheng YJ, Tsai MH, Chiang CJ, *et al.* Ajuvant radiotherapy after curative surgery for oral cavity squamous cell carcinoma and treatment effect of timing and duration outcomes — A Taiwan Cancer Registry national database analysis. Caner Med 2018; **7**: 3073–83.

11. Rizvi ZH, Alonso JE, Kuan EC, *et al.* Treatment outcomes of patients with primary squamous cell carcinoma of the retromolar trigone. Laryngoscope 2018; **128**: 2740–4.

12. Ishikawa T, Monden N, Takishita T, *et al.* Surgical site infection results in a poor prognosis for oral cancer patients. Jpn J Head Neck Cancer 2013; **39**: 379–84.

13. Beecher SM, O'Leary DP, McLaughlin, *et al.* The impact of surgical complications on cancer recurrent rates: a literature review. Oncol Res Treat 2018; **41**: 478–82.

14. Evans M, Beasley M. Target delineation for postoperative treatment of head and neck cancer. Oral Oncol 2018; **86**: 288–95.

15. Jardim JF, Francisco AL, Gondak R, *et al.* Prognostic impact of perineural invasion and limphovascular invasion in advanced stage oral squamous cell carcinoma. Int J Oral Maxillofac Surg 2015; **44**: 23–8.

16. Murakami R, Nakayama H, Semba A, *et al.* Prognostic impact of the level of nodal involvement: retrospective analysis of patients with advanced oral squamous cell carcinoma. Br J Oral Maxillofac Surg 2017; **55**: 50–5.

17. Hasegawa T, Shibuya Y, Takeda D, *et al.* Prognosis of oral squamous cell carcinoma patients with level IV/V metastasis: An observational study. J Cranio-Maxillofac Surg 2017; **45**: 145–9.