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Original Article

Persisting Gaps in Optimal Care of Stage III Non-small Cell Lung Cancer: An Australian Patterns of Care Analysis

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Abstract

Background: Wide variation exists globally in the treatment and outcomes of stage III patients with non–small cell lung cancer (NSCLC). We conducted an up-to-date patterns of care analysis in the state of Victoria, Australia, with a particular focus on the proportion of patients receiving treatment with radical intent, treatment trends over time, and survival.

Materials and Methods: Stage III patients with NSCLC were identified in the Victorian Lung Cancer Registry and categorized by treatment received and treatment intent. Logistic regression was used to explore factors predictive of receipt of radical treatment and the treatment trends over time. Cox regression was used to explore variables associated with overall survival (OS). Covariates evaluated included age, sex, ECOG performance status, smoking status, year of diagnosis, Australian born, Aboriginal or Torres Strait Islander status, socioeconomic status, rurality, public/private status of notifying institution, and multidisciplinary meeting discussion.

Results: A total of 1396 patients were diagnosed between 2012 and 2019 and received treatment with radical intent 67%, palliative intent 23%, unknown intent 5% and no treatment 5%. Radical intent treatment was less likely if patients were >75 years, ECOG ≥1, had T3-4 or N3 disease or resided rurally. Surgery use decreased over time, while concurrent chemoradiotherapy and immunotherapy use increased. Median OS was 38.0, 11.1, and 4.4 months following radical treatment, palliative treatment or no treatment, respectively.

Conclusion: Almost a third of stage III patients with NSCLC still do not receive radical treatment. Strategies to facilitate radical treatment and better support decision making between increasing multimodality options are required.

Key words: stage III NSCLC; patterns of care; elderly; concurrent chemoradiotherapy; adjuvant immunotherapy; unwarranted variation.

Implications for Practice

Whilst the proportion of patients receiving active treatment appears higher in Australia than other developed countries, we highlight that a third of patients still do not receive radical treatment and was more likely if patients were older, frailer, had more advanced disease or resided rurally. Increased clinician decision-making strategies, as well as improved patient assessment and support throughout their care may facilitate increased use of radical treatments.

Introduction

The management of patients with stage III NSCLC can be challenging for clinicians, with guideline-based treatment pathways often complicated by a range of objective and subjective patient-related factors. These locally advanced tumors present heterogeneously with a range of treatment options often associated with substantial toxicity and treatment intolerance. The broader provision of radical intent treatment with improved tolerability in locally advanced NSCLC is a significant area of current interest.

Current guidelines recommend definitive concurrent chemoradiotherapy with consolidative immunotherapy, and surgery with adjuvant chemotherapy or neoadjuvant immunotherapy and chemotherapy in a small subset of fit patients with resectable disease.[1-4] Concurrent chemoradiotherapy is associated with significant toxicity and as elderly patients were under-represented in the foundational clinical trials[5] this treatment has been generally preferred for those of good performance status and under 70 years of age.[6-8] Given the median age at diagnosis of 71[9] and the highest prevalence

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of comorbidities at presentation in patients with lung cancer compared with other cancers,[10] patients with stage III NSCLC are often deemed ineligible for standard-of-care multi-modality treatment.[11] There are wide global variations in the number of patients receiving active treatment: a US study of over 246,000 patients with stage III NSCLC in the National Cancer Database between 2008 and 2012 found 16.3% of stage IIIA and 22.3% of stage IIIB patients go untreated[12]; an audit of stage III patients with NSCLC diagnosed in England in 2016 found 36% received no cancer treatment and 34% received treatment with palliative intent.[13]

Analyses of Australian patients with lung cancer have been reported for those diagnosed in the 1990s and early 2000s[6,14-17] but contemporary studies are lacking. There have been significant improvements in diagnosis, staging and treatment of lung cancer in the past 2 decades, and an up-to-date analysis of the Australian population is overdue. This population-based study aimed to explore the patterns of care in patients with stage III NSCLC in the Australian state of Victoria. We identified the number of patients diagnosed and the factors associated with receiving radical intent treatment, explored trends over time and survival outcomes.

Materials and Methods

Databases

The Victorian Lung Cancer Registry (VLCR) was established in 2011 to monitor and report on quality of care and patient outcomes.[18] The VLCR case ascertainment includes over 85% of all newly diagnosed primary lung cancers in Victoria, Australia (population 6.68 million). Patients are notified to the VLCR through hospital discharge data as reported by participating public and private institutions around the state. Demographic, diagnostic, disease, clinical, and treatment-related information are prospectively collected for all newly diagnosed consented adults. The VLCR uses an "opt-out" consent model, where clinical data are collected and included in the registry platform unless patients call a toll-free number to opt-out—approximately 3.5% of patients have done so.

Detailed radiotherapy information was obtained through linkage with The Victorian Radiotherapy Minimum Data Set (VRMDS). The VRMDS was established in 2008 as an initiative of the Victorian government's Department of Health and Human Services (DHHS) in collaboration with Victorian radiotherapy providers to collect radiotherapy data to inform future service planning. Data matching between the VLCR and VRMDS were carried out by the Centre for Victorian Data Linkage. Death data were updated via the Registry of Births, Deaths and Marriages Victoria. Cause of death details were unavailable.

Ethics approval for this study was obtained from Monash University Human Research Ethics Committee (Project ID:22601).

Study Population

Patients diagnosed with stage III NSCLC between 2012 and 2019 were included. As the American Joint Committee on Cancer (AJCC) stage classification of lung cancer was updated during this time period,[19] staging was standardized for all patients and re-calculated to conform to the eighth edition. Patients with insufficient data to complete staging were excluded.

Treatment Definitions

Surgery and systemic therapy details were obtained from the VLCR. Systemic therapy was subcategorised into cytotoxic agents or immunotherapy. Radiotherapy was defined as any record of lung or mediastinal radiotherapy in either the VLCR or VRMDS. *Concurrent chemoradiotherapy* was defined as start dates of systemic therapy and radiotherapy to the chest or mediastinum occurring within 30 days of each other, and *sequential chemoradiotherapy* was defined as start dates greater than 30 days, but less than 90 days of one another. *Radiotherapy alone* was defined as radiotherapy delivered without any other modality or radiotherapy delivered with a subsequent treatment of systemic therapy more than 90 days after radiotherapy commenced. *No treatment* was defined as no record of surgery, systemic therapy or radiotherapy to the lung or mediastinum in either dataset. Treatment intent was defined as *radical* if: any surgical resection performed (as a single or multimodality treatment); radiotherapy where ≥20 fractions were delivered with or without systemic therapy; or radiotherapy where <20 fractions were delivered and treatment technique was classified as stereotactic. *Palliative* treatment was defined as: systemic therapy alone or radiotherapy with <20 prescribed fractions. *Unknown* treatment intent was defined as radiotherapy (alone or combined with systemic therapy) where the number of fractions was unknown. Radiotherapy fractions, instead of prescribed dose, was used in these definitions as prescribed dose was not recorded in the VRMDS until 2017. Twenty fractions was chosen as the cut-off point to include radical accelerated hypofractionated regimes such as 55 Gy in 20 fractions[20] which were present in our series.

Covariates

Patient variables evaluated were: age at diagnosis, sex, Eastern Co-operative Oncology Group (ECOG) performance status, smoking status, whether their case was discussed at a multidisciplinary meeting (MDM), year of diagnosis, Australian born, Aboriginal or Torres Strait Islander status, socioeconomic status, public/private status of notifying institution and rurality. Socioeconomic status was defined by the Australian Bureau of Statistics' Index of Relative Socio-economic Disadvantage (IRSD) from the 2016 Australian Census[21] and linked against Statistical Area 1 (SA1) regions as outlined in the Australian Statistical Geography Standard (2016)[22] for patient residence at time of reporting. SA1 regions are the smallest geographical units for which census data is available, each having a population of between 200 and 800 people.[22] IRSD scores were divided into quintiles (based on the census data) where quintile 1 corresponds to the most disadvantaged and quintile 5 the least disadvantaged. Comorbidity was not analysed due to a paucity of data.

Statistical Analysis

Descriptive statistics were used to describe the population and the distribution of treatment types between staging groups. Logistic regression was used to explore factors predictive of receipt of radical treatment and the trends of each treatment type delivered by year of diagnosis. A Mann-Whitney U test or Kruskall Wallis test were used to compare variables between rural and metro patients who did not receive treatment. Overall survival was measured from the date of diagnosis and was analyzed using the

Kaplan-Meier method and compared between treatment groups and between treatment intentions using a log-rank test. A Cox proportional hazards regression/model was used to explore variables associated with overall survival. Variables were included in multivariate analyses if they had a *P*-value of < .05 in the univariate analysis. *Notifying institution sector* was excluded from the multivariate analysis, due to confounding with other variables and was felt to be less clinically relevant due to the fact the public/private status of the notifying institution did not necessarily represent the institution where treatment was delivered. All statistical analyses were carried out in the R statistical programming environment (v4.0.3).[23] *P*-values of <.05 were considered statistically significant.

Results

Population Demographics

Between 2012 and 2019, 8449 patients with NSCLC were captured by the VLCR, of which 5907 had completed TNM data to classify by stage. A total of 1396 patients were classified as stage III, of which 55.3% were IIIA, 35.2% IIIB, and 9.5% IIIC. The median age at diagnosis was 69 years (range: 23-96), 62.9% were male, 89.6% were current or ex-smokers and 82.7% were discussed in an MDM. Of those with ECOG recorded (*n* = 1012), 84.3% had an ECOG of 0 or 1. Positron emission tomography (PET) was performed in 67.8% of patients, although rates increased from 4% in 2012, 44% in 2015 to 85% in 2019. Table 1 summarizes the patient demographics.

Table 1. Summary of patient demographics (*n* = 1396).

	n (%)
Sex	
Female	518 (37.1)
Male	878 (62.9)
Age	
≤60	321 (23.0)
61-65	196 (14.0)
66-70	268 (19.2)
71-75	264 (18.9)
76-80	194 (13.9)
≥80	153 (11.0)
Stage	
IIIA	772 (55.3)
IIIB	491 (35.2)
IIIC	133 (9.5)
ECOG	
0	409 (29.3)
1	444 (31.8)
2	121 (8.7)
3	34 (2.4)
4	4 (0.3)
Unknown	384 (27.5)
Weight loss	
Yes	578 (41.4)
No	511 (36.6)
Unknown	307 (22.0)
Discussed at MDM	
Yes	1154 (82.7)
No	242 (17.3)
Smoking status	
Current	470 (33.7)
Ex	781 (55.9)
Never	112 (8.0)
Unknown	33 (2.4)
Diagnostic technique	
Histology	979 (70.1)
Cytology	368 (26.4)
Clinical	40 (2.9)
Unknown	9 (0.6)
PET performed	
Yes	947 (67.8)
No	449 (32.2)

Treatment Intent

Treatment intent was radical for 934 (66.9%) patients, palliative for 322 (23.1%), unknown for 64 (4.6%) and 76 (5.4%) received no treatment. On univariate logistic regression analysis, younger age, lower ECOG, lower T-stage, lower N-stage, residence in metropolitan Melbourne, higher socioeconomic status and treatment in a private institution were associated with increased receipt of radical treatment. On multivariate analysis, age, ECOG, T-stage, N-stage, and residence in metropolitan Melbourne remained statistically significant (Table 2). When comparing features between metropolitan and rural patients who did not receive treatment there was no difference in age (*P* = 3.075), ECOG (*P* = .112) or stage distribution (*P* = .457), although rural location was associated with greater socioeconomic disadvantage (*P* < .001).

Treatments

A summary of the treatments delivered by stage is shown in Table 3.

Surgery

Surgery was performed in 420 (30.1%) patients, the majority of whom had stage IIIA disease (76.7%) (stage IIIB 22.3%, stage IIIC (1.0%). Of those with procedure details available (*n* = 400), 367 had a single resection procedure (71.1% lobectomy, 13.4% pneumonectomy, 9.5% wedge resection, 6% segmentectomy) and 33 required multiple resections as part of their treatment course. 2.7% received neoadjuvant chemotherapy, 0.7% neoadjuvant radiotherapy, 36.4% adjuvant chemotherapy, 5.6% adjuvant radiotherapy, and 25.7% trimodality treatment (any sequencing of the three).

Radical Chemoradiotherapy

Radical chemoradiotherapy was delivered to 427 (30.6%) patients, 97.2% of which was given concurrently and 2.8% sequentially. From 2017 onward, Durvalumab was delivered in 72 out of 302 (23.8%) patients. The distribution of stage in those receiving radical chemoradiotherapy was 48.7% IIIA, 41.2% IIIB, 10.1% IIIC. Radiotherapy was delivered in 30 fractions for 332 (77.8%) patients, 20-29 fractions for 73 (17.1%) patients, and 31-33 fractions for 22 (5.2%) patients.

Table 2. Logistic regression to identify factors contributing to receipt of radical treatment.

	n	% radical	Univariate			Multivariate[b]		
			OR (CI)	*Z* value	*P*-value	OR (CI)	*Z* value	*P*-value
Sex					.397			
Female	518	68.3	1 (Ref)					
Male	878	66.1	0.90 (0.72-1.14)	−0.846	.398			
Age (years)					**<.001**			**<.001**
≤60	321	75.4	1 (Ref)			1 (Ref)		
61-65	196	70.4	0.78 (0.52-1.16)	−1.244	.213	0.69 (0.41, 1.19)	−1.344	.179
66-70	268	71.6	0.84 (0.58-1.21)	−0.955	.340	0.94 (0.57, 1.58)	−0.223	.823
71-75	264	69.3	0.74 (0.51-1.06)	−1.637	.102	0.74 (0.45, 1.20)	−1.212	.226
76-80	194	59.3	0.48 (0.32-0.70)	−3.809	**<.001**	0.47 (0.27, 0.79)	−2.838	**.005**
≥81	153	41.8	0.23 (0.15-0.35)	−6.937	**<.001**	0.25 (0.14, 0.43)	−4.852	**<.001**
ECOG					**<.001**			**<.001**
0	409	77.8	1 (Ref)			1 (Ref)		
1	444	64.0	0.51 (0.38-0.69)	−4.337	**<.001**	0.63 (0.44, 0.89)	−2.628	.009
2	121	41.3	0.20 (0.13-0.31)	−7.295	**<.001**	0.25 (0.15, 0.41)	−5.475	**<.001**
3	34	17.6	0.06 (0.02-0.14)	−6.000	**<.001**	0.07 (0.02, 0.17)	−5.134	**<.001**
4	4	25.0	0.10 (0.00-0.75)	−2.024	**.024**	0.06 (0.00, 0.62)	−2.232	**.026**
Discussed at MDM					.766			
No	242	67.8	1 (Ref)					
Yes	1154	66.7	0.96 (0.71-1.28)	−0.297	.767			
Australian born					.319			
No	528	68.8	1 (Ref)					
Yes	868	65.9	0.89 (0.70-1.12)	−0.996	.319			
Aboriginal and/or TSI					.407			
No	1377	67.0	1 (Ref)					
Yes	19	57.9	0.67 (0.27-1.75)	−0.840	.401			
T-stage[a]					**.001**			**.033**
0-1	207	78.3	1(Ref)			1 (Ref)		
2	368	68.5	0.61 (0.41, 0.90)	−2.450	**.014**	0.69 (0.41, 1.15)	−1.409	.159
3	353	65.2	0.52 (0.35, 0.77)	−3.240	**.001**	0.47 (0.27, 0.80)	−2.756	**.006**
4	441	63.3	0.48 (0.32, 0.70)	−3.775	**<.001**	0.53 (0.31, 0.92)	−2.229	**.026**
N Stage					**<.001**			**<.001**
0	142	73.2	1 (Ref)			1 (Ref)		
1	177	74.0	1.04 (0.63-1.72)	0.156	.876	1.06 (0.52, 2.20)	0.170	.865
2	783	72.2	0.95 (0.63-1.41)	−0.242	.808	0.70 (0.38, 1.27)	−1.156	.248
3	285	45.3	0.30 (0.19-0.47)	−5.347	**<.001**	0.17 (0.09, 0.33)	−5.266	**<.001**
Notifying Institution Sector					**<.001**			
Private	208	76.4	1 (Ref)					
Public	1188	65.2	0.58 (0.41-0.81)	−3.126	**.002**			
Rurality (SA-GCC)					**<.001**			**.023**
Metropolitan Melbourne	842	69.5	1 (Ref)			1 (Ref)		
Regional Victoria	462	59.3	0.64 (0.50-0.81)	−3.736	**<.001**	0.67 (0.48, 0.95)	−2.281	**.023**
IRSD Quintiles					**<.001**			.320
1 (Most disadvantaged)	336	57.7	1 (Ref)			1 (Ref)		
2	281	69.4	1.66 (1.19, 2.32)	2.977	**.003**	1.60 (1.03, 2.51)	2.071	.038
3	256	65.9	1.41 (1.01, 1.98)	2.010	**.044**	1.09 (0.69, 1.71)	0.363	.716
4	228	71.1	1.80 (1.26, 2.58)	3.200	**.001**	1.22 (0.75, 1.99)	0.789	.430
5 (Least disadvantaged)	198	69.7	1.68 (1.16, 2.45)	2.741	**.006**	1.28 (0.75, 2.22)	0.894	.372
Unknown	97	79.4	2.82 (1.68, 4.93)	3.778	**<.001**	4.84 (0.33,126.33)	1.129	.259

Bold values indicate statistical significance.
[a]T0 and T1 combined due to small number of T0 ($n = 3$).
[b]*P*-values in multivariate model come from the fit of the model with all 6 predictors.
Abbreviations: MDM, multidisciplinary meeting; TSI, Torres strait islander; T, tumor; N, nodal; SA, statistical area; GCC, greater capital city; IRSD, Index of Relative Socio-economic Disadvantage.

Table 3. Treatments delivered by disease stage (n = 1396).

	Stage IIIA (n = 772), n (%)			Stage IIIB (n = 491), n (%)			Stage IIIC (n = 133), n (%)			All Stage III (n = 1396), n (%)		
	Radical	Palliative	Unknown	Radical	Palliative	Unknown	Radical	Palliative	Unknown	Radical	Palliative	Unknown
Single modality												
Surgery alone	94 (12.2)	—	—	24 (4.9)	—	—	1 (0.8)	—	—	119 (8.5)	—	—
Systemic therapy alone	—	41 (5.3)	—	—	55 (11.2)	—	—	21 (15.8)	—	—	117 (8.4)	—
RT alone	57 (7.4)	59 (7.6)	12 (1.6)	20 (4.1)	60 (12.2)	10 (2.0)	10 (7.5)	26 (19.5)	3 (2.3)	87 (6.2)	145 (10.4)	25 (1.8)
Multimodality												
Surgery+ Systemic	133 (17.2)	—	—	33 (6.7)	—	—	0 (0)	—	—	166 (11.9)	—	—
Surgery+RT	25 (3.2)	—	—	4 (0.8)	—	—	0 (0)	—	—	29 (2.1)	—	—
Concurrent ChemoRT	204 (26.4)	11 (1.4)	19 (2.5)	169 (34.4)	19 (3.9)	14 (2.9)	42 (31.6)	3 (2.3)	0 (0)	415 (29.7)	33 (2.4)	33 (2.4)
Sequential ChemoRT	4 (0.5)	7 (0.9)	2 (0.3)	7 (1.4)	11 (2.2)	3 (0.6)	1 (0.8)	9 (6.8)	1 (0.8)	12 (0.9)	27 (1.9)	6 (0.4)
Surgery+ Systemic+RT	70 (9.1)	—	—	33 (6.7)	—	—	3 (2.3)	—	—	106 (7.6)	—	—
Total	587 (76.0)	118 (15.3)	33 (4.3)	290 (59.1)	145 (29.5)	27 (5.5)	57 (42.9)	59 (44.4)	4 (3.0)	934 (66.9)	322 (23.1)	64 (4.6)
No treatment	34 (4.4)			29 (5.9)			13 (9.8)			76 (5.4)		

Radical Radiotherapy Alone

Radical radiotherapy alone was delivered to 87 (6.2%) patients with 47 (54%) receiving 30 fractions, 38 (43.7%) receiving 20-29 fractions, and 2 (2.3%) receiving 33 fractions.

Palliative Treatment

Of those who received palliative treatment (n = 322), 45% received radiotherapy alone, 36.3% received systemic therapy alone, and 18.6% chemoradiotherapy. 62.4% of those treated with radiotherapy alone, received 10-19 fractions.

Trends Over Time

Evaluation of temporal trends in patterns of delivered treatments revealed a decline in the use of surgical treatments, whilst the use of chemotherapy, immunotherapy, concurrent chemoradiotherapy, and radiotherapy (any) increased (Table 4). Neither the proportion of patients receiving radical treatment nor the number of patients going untreated changed over time. In 2012, 72%, 19%, and 5% of patients received radical, palliative or no treatment respectively, compared to 72%, 21%, and 4% in 2019. The use of older 2D/3D radiotherapy techniques reduced from 90% to 20% (P < .001) over the time period, whilst the use of more modern techniques, IMRT/VMAT, increased from 3% to 76% (P < .001). Supplementary Fig. S1 demonstrates the proportions of radical treatment types, palliative treatment, and no treatment per year.

Overall Survival

Kaplan-Meier curves for overall survival by treatment intent, radical treatment type, and disease stage are shown in Figs. 1-3, respectively. The median overall survival (OS) for all patients with stage III NSCLC was 25.1 months (95% CI: 21.6-27.5 months) and 31.2 months (95% CI: 27.8-37.9 months), 19.5 months (95% CI: 17.0-21.5 months), 17.5 months (95% CI: 11.8-27.1 months) for stages IIIA, IIIB, and IIIC, respectively. OS was longer following radical treatment (38.0 months, 95% CI: 32.9-45.7 months) compared with palliative treatment (11.1 months, 95% CI: 9.3-13.5 months) or no treatment (4.4 months, 95% CI: 2.4-8.0 months) (P < .001). The 1-year overall survival rate for patients with stage III NSCLC was 68.3% (95% CI: 65.9-70.8%). When stratified by treatment intent 1-year survival rates were 79.6% (95% CI: 77.0-82.2%), 46.9% (95% CI: 41.8-52.7%), and 25.3% (95% CI: 17.2-37.4%) for radical, palliative, and no treatment. When adjusted for age, ECOG, smoking status, T-stage, N-stage, and socioeconomic status, radical treatment was associated with longer survival (HR 0.49 [95% CI: 0.41-0.58], P < .001). A full summary of the univariate and multivariate results can be found in Table 5.

Table 4. Univariate logistic regression analysis of trends in treatments delivered between 2012 and 2019.

Treatment	OR(CI)	Z-value	P-value
Surgery	0.89 (0.84, 0.94)	−4.346	**<.001**
Chemotherapy	1.07 (1.02, 1.13)	2.611	**.009**
Immunotherapy	1.54 (1.39, 1.73)	7.818	**<.001**
Concurrent ChemoRT	1.21 (1.15, 1.29)	6.484	**<.001**
Sequential ChemoRT	0.90 (0.79, 1.04)	−1.458	.145
Radiotherapy (any)	1.09 (1.03, 1.16)	2.871	**.004**
Radical radiotherapy alone	1.01 (0.91, 1.13)	0.174	.862
Palliative radiotherapy	0.97 (0.90, 1.04)	−0.838	.402
Radiotherapy (2D/3D)	0.73 (0.69, 0.77)	−10.89	**<.001**
Radiotherapy (IMRT/VMAT)	1.83 (1.68, 2.00)	13.28	**<.001**
Treatment intent			
Radical treatment	1.05 (0.99, 1.11)	1.752	.080
Palliative treatment	0.95 (0.89, 1.01)	−1.740	.082
No treatment	0.98 (0.88, 1.10)	−0.344	.731

Bold values indicate statistical significance. Odds ratio (OR) refers to the estimated change after a period of 1 year.

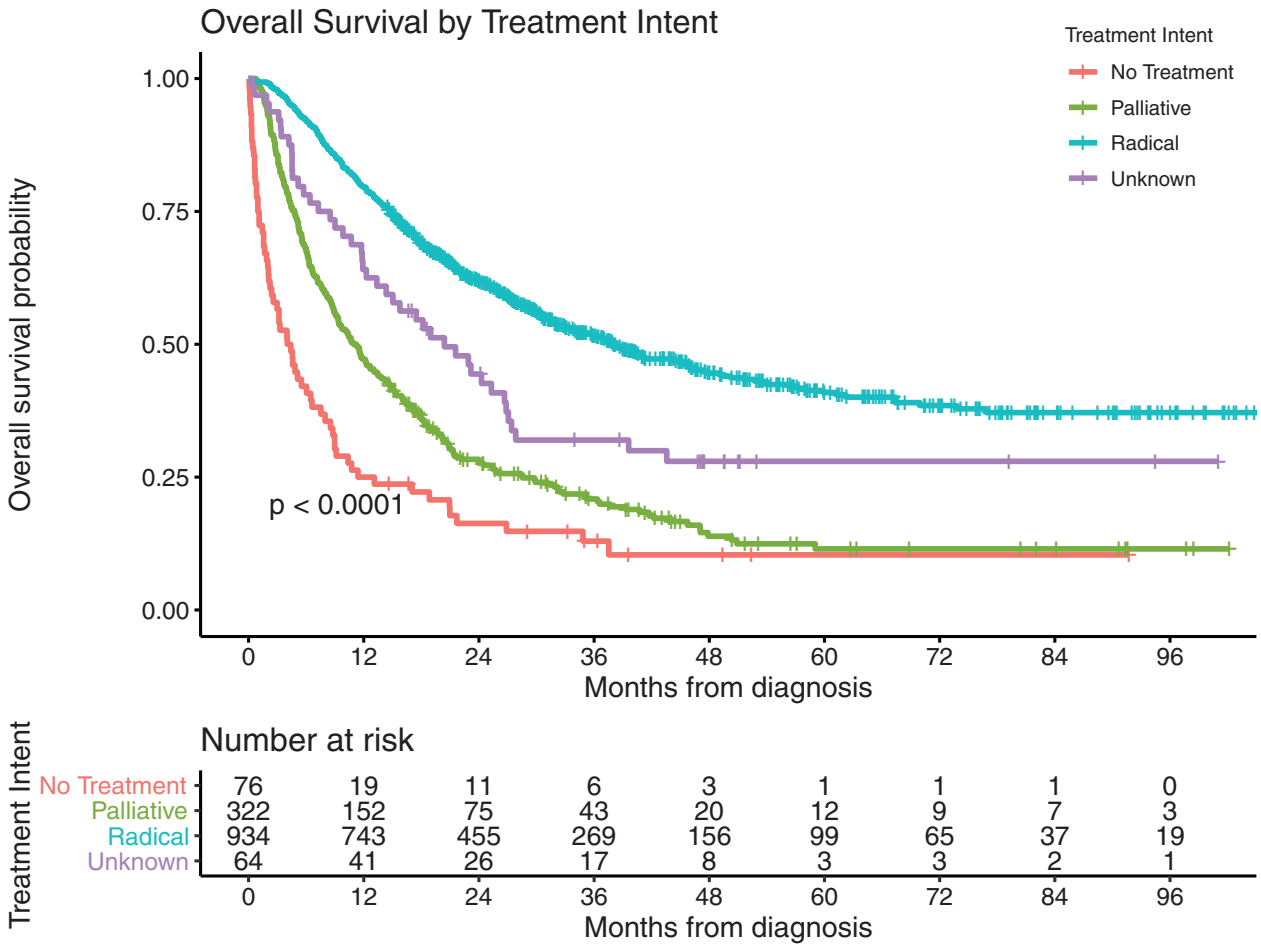

Figure 1. Kaplan-Meier survival curves by treatment intent.

When comparing survival curves by radical treatment type (Fig. 2), surgery (alone and as a combined modality) provided the longest OS with a 5-year survival rate of 49.6% (95% CI:44.1-59.9%). The addition of durvalumab to concurrent chemoradiotherapy improved survival on log-rank test (P < .001), increasing 1-year and 2-year survival rates from 75.8% (95% CI: 71.4-80.5%) to 90.3% (95% CI: 83.7% - 97.4%) and 55.2% (95% CI: 50.0-60.8%) to 81.8% (72.9-91.8%), respectively. Durvalumab data were not mature enough to determine median OS. Kaplan-Meier curves for radical treatment type by disease stage are presented in Supplementary Figs. S2-S4.

Discussion

Almost a third of patients with stage III NSCLC did not receive radical treatment and this proportion was unchanged over the 8-year time period. Patients were less likely to receive radical treatment if they were over the age of 75, ECOG 1 or above, had T3-4 or N3 disease or of rural residence. The use of surgery decreased over time, counterbalanced by an increase in use of concurrent chemoradiotherapy. The most dramatic changes in practice were the introduction of adjuvant immunotherapy and the transition to intensity modulated radiotherapy techniques.

Whilst the rate of patients going untreated (5%) did not change over the 8-year time period, it was noticeably improved compared with previous studies from earlier time periods. Analyses on the Australian population in the 1990s and early 2000s reported no treatment in 20%-30% of patients with stage III NSCLC,[6,14-17] similar to more recent international reports[12,13,24-26] (Supplementary Table S1). Reasons for this rise in active treatment over the last 2-3 decades and the disparity between international reports could be the higher surgical rates compared to other countries, high rates of tissue diagnosis, 84% of patients having a reasonable ECOG of 0-1, the smaller geographical area of Victoria compared with larger states and countries or the free and universal healthcare provided by the Australian Government. Surprisingly 9% of patients had surgery alone, despite guidelines recommending adjuvant chemotherapy following complete resection.[27] Only 30% of patients received the guideline recommended treatment of concurrent chemoradiotherapy for unresected stage III NSCLC, although a slight increase in rates per year was observed. Given the significant increase in use of more advanced radiotherapy techniques (IMRT/VMAT), it was surprising that this did not translate into an increase in radical intent treatments which has been reported at other institutions alongside improvements in survival.[28] These techniques allow for safer delivery of radiotherapy to larger treatment volumes, which would previously have been treated with palliative radiotherapy; however, we found no change in the palliative radiotherapy rates over time. Perhaps this is due to the already high radical treatment rates and may have instead

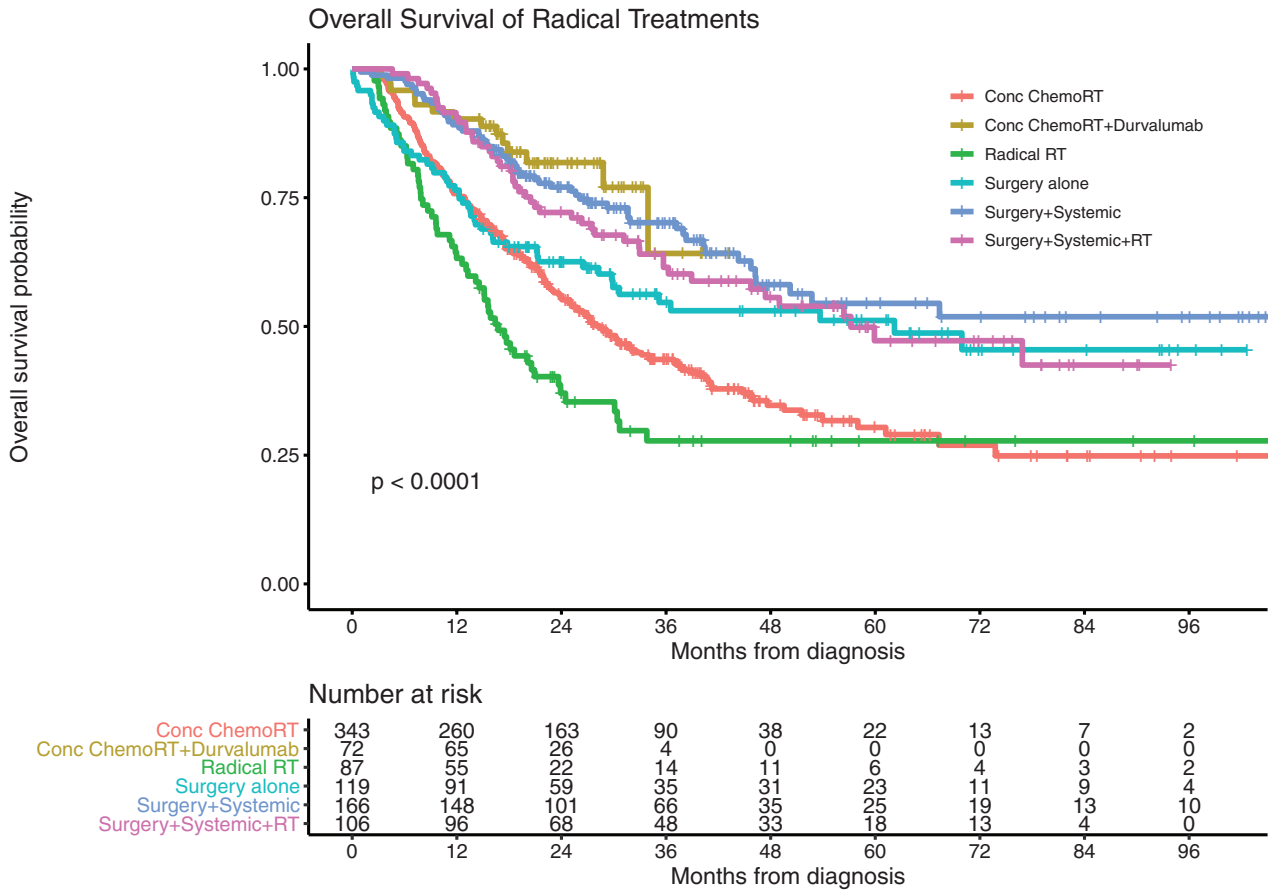

Figure 2. Kaplan-Meier survival curves by radical treatment type.

led to the increase in chemoradiotherapy and reduction in surgery.

We confirm a significant increase in use of immunotherapy in the latter years of the time period, coinciding with the release of the PACIFIC trial results in 2017 showing improvements in progression-free survival (and OS in subsequent reports) with the use of consolidation durvalumab after chemoradiotherapy.[4,29,30] Our data confirm that the benefit of adjuvant durvalumab with survival outcomes within the first 3 years from diagnosis similar to that of surgery. This may have contributed to the shift in practice from surgery to chemoradiotherapy, alongside improved chemotherapy practices increasing tolerability,[31] and the increased use of highly conformal modulated radiotherapy techniques which improve normal tissue sparing and minimize toxicity.[32] With evidence emerging on the benefit of adjuvant and neoadjuvant immunotherapy with surgery,[3,33,34] practice may shift again in the future.

Of the independent factors identified to negatively influence the likelihood of receiving radical treatment, increasing age is of particular concern, with only 42% of those aged over 80 received radical treatment compared to 75% of those aged under 60. This disparity is partly driven by concern of increased treatment-related toxicity, with our previous work demonstrating a 28% increase in mortality risk in stage III/IV disease for patients aged over 80 compared with younger patients and a significantly reduced likelihood of both presentation of these patients to an MDM and receipt of treatment (OR 0.24).[35] Additionally, it is unclear if concurrent chemoradiotherapy for unresectable stage III NSCLC in elderly patients is appropriate given that older patients and those of poor performance were excluded from the foundational clinical trials.[5] Whilst survival improvements in elderly patients following chemoradiotherapy have been reported with outcomes comparable to younger patients,[8,36,37] acute toxicities were worse,[36] especially for concurrent treatment where one series reported unplanned hospitalisation in 74% of elderly patients receiving concurrent chemoradiotherapy.[38] Sequential regimes may provide improved treatment tolerability and safety, with 2 population-based studies reporting a survival advantage over concurrent treatment.[37,39]

Geographical distance is a clear barrier to treatment, with only 59% of rural patients receiving radical treatment compared with 70% in metropolitan areas and supports others reports.[40,41] A reduced number of hospital attendances are more convenient and less burdensome for these older, frailer patients and their families, particularly if they live far from a radiotherapy centre. Certainly, when given a choice 45% of patients with advanced lung cancer chose a shorter radiotherapy course, despite knowing it was associated with worse survival, claiming the shorter duration as their highest priority.[42] This has given impetus to the investigation of novel hypofractionated radiotherapy regimens,[43-47] with recent work suggesting the potential for similar outcomes to conventional treatment courses.[48]

The optimal management of patients who are older, of poorer performance status or ineligible for surgery or radical chemoradiotherapy is complex. Palliative radiotherapy alone

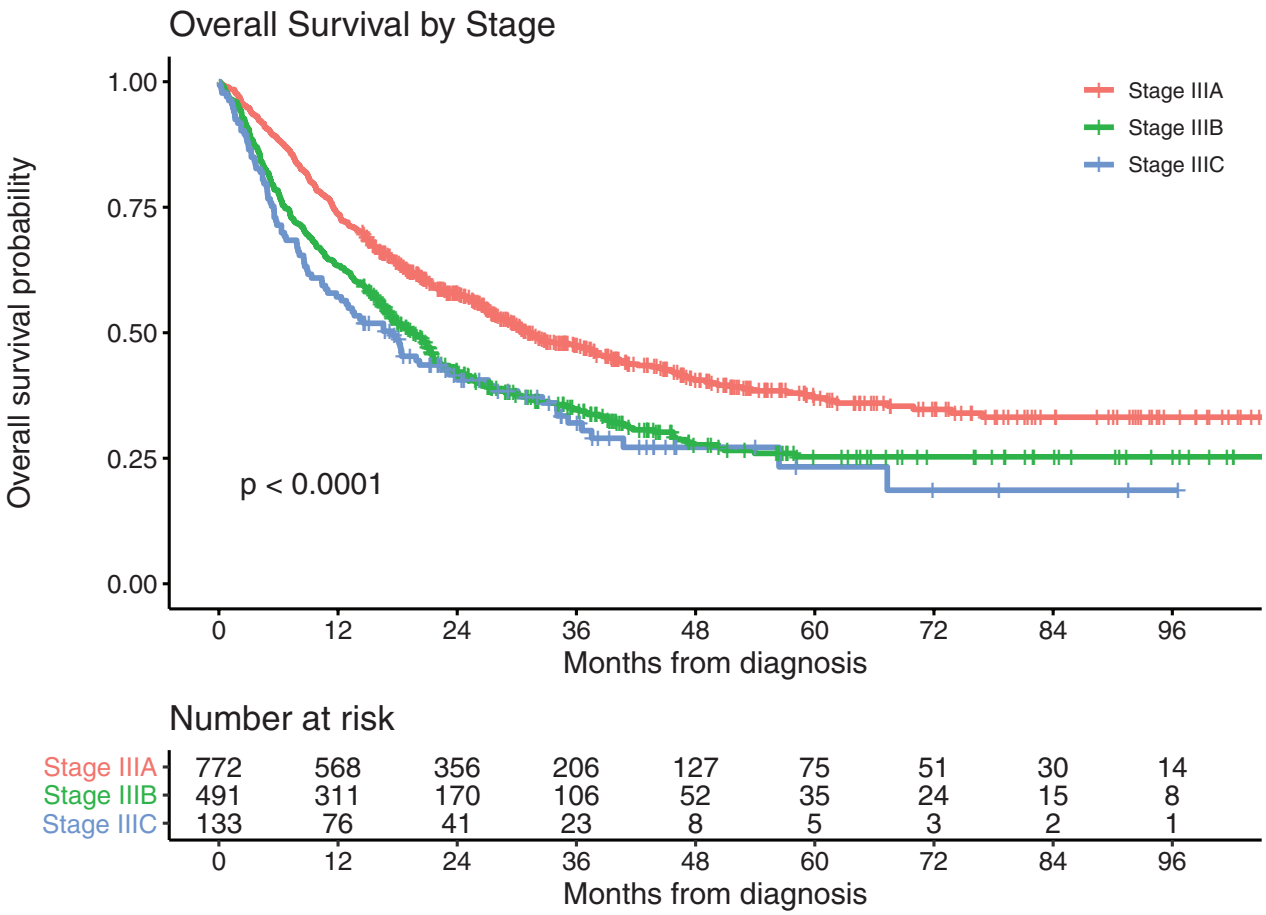

Figure 3. Kaplan-Meier survival curves by disease stage.

(45%) and systemic therapy alone (36%) were the most common treatments for these patients. The heterogenous nature of this group of patients and the wide range of palliative treatment options and combinations requires careful personalization of therapy and does not lend itself well to guideline-based practice. The incorporation of instruments to enhance clinician's decision-making abilities, such as frailty[49] and geriatric assessment tools,[50] should be investigated. Furthermore, increasing resources aimed at improving patient's access and tolerability of definitive treatments, such as through dedicated lung cancer nurses[51] and smoking cessation strategies,[52] is also likely to provide benefits.

This study has a number of limitations. Firstly, all patients were reclassified in line with the eighth edition of the AJCC lung cancer staging. While the factors determining stage III disease as a whole has not changed between editions, some patients may have been upstaged to a higher sub-group (A, B, or C) in this report compared to their original diagnosis. Secondly, there is selection bias inherent in the VLCR data: patients are only registered after presentation to hospital for an invasive procedure or for an inpatient admission; patients with a clinical diagnosis of lung cancer (ie, based on imaging alone) and who did not go on to receive treatment would not be captured skewing the data toward patients well enough for treatment. Conversely, while the VLCR generally has good coverage of both public and private institutions, one large multi-site private institution did not report to the VLCR during this time period. The inclusion of this institution could also affect the results, although presumably in the opposite direction, given that private patients have been found to be more likely to receive treatment. As with any registry study, the lack of complete data were a challenge, with a significant proportion of patients excluded due to incomplete TNM staging data. It is possible patients with stage III NSCLC may be overrepresented in the excluded un-staged group. Comorbidity was not analyzed due to a paucity of data, while ECOG was unavailable for 28% of patients and hence these patients were excluded from the univariate and multivariate analyses. The collection of systemic therapy details in the VLCR has evolved and expanded over the study period, making analysis difficult. Finally, these results describe the state of Victoria and may not necessarily be representative of the rest of Australia due to the significant geographical variations between states.

While these results from an Australian population are promising and indeed better than those of other developed countries, we have shown that up to a third of patients with stage III NSCLC do not receive radical treatment and this has not improved over time. Alternative treatment solutions are needed for patients who are ineligible or unwilling to undergo surgery or a long course of radiotherapy with or without chemotherapy, with the potential to improve survival in these patients. Increased clinician decision-making strategies, as well as improved patient assessment and support throughout their care may facilitate increased use of

Table 5. Cox proportional hazard analysis of survival.

	Univariate			Multivariate [b]		
	HR (CI)	*Z*-value	*P*-value	HR (CI)	*Z*-value	*P*-value
Sex			.083			
Female	1 (Ref)					
Male	1.13 (0.98, 1.31)	1.726	.084			
Age (years)			**<.001**			**<.001**
≤60	1 (Ref)			1 (Ref)		
61-65	1.29 (1.01, 1.64)	2.045	**.041**	1.19 (0.89, 1.61)	1.168	.243
66-70	1.37 (1.10, 1.70)	2.770	**.006**	1.44 (1.09, 1.89)	2.593	**.010**
71-75	1.33 (1.06, 1.67)	2.498	**.013**	1.20 (0.91, 1.59)	1.296	.195
76-80	1.87 (1.49, 2.36)	5.325	**<.001**	1.59 (1.18, 2.12)	3.103	**.002**
≥81	2.30 (1.81, 2.93)	6.765	**<.001**	2.15 (1.59, 2.92)	4.912	**<.001**
ECOG			**<.001**			**<.001**
0	1 (Ref)			1 (Ref)		
1	1.43 (1.20, 1.72)	3.886	**<.001**	1.16 (0.96, 1.41)	1.540	.123
2	2.28 (1.78, 2.92)	6.518	**<.001**	1.52 (1.16, 2.00)	3.029	**.002**
3	3.68 (2.51, 5.41)	6.639	**<.001**	2.04 (1.35, 3.09)	3.363	**<.001**
4	10.53 (3.88, 28.59)	4.620	**<.001**	5.40 (1.94, 15.02)	3.234	**.001**
Discussed at MDM			.543			
No	1 (Ref)					
Yes	0.95 (0.79, 1.13)	−0.613	.540			
Smoking status			**<.001**			**<.001**
Current	1 (Ref)			1 (Ref)		
Ex	0.92 (0.80, 1.07)	−1.101	.271	0.86 (0.72, 1.03)	−1.612	.107
Never	0.41 (0.30, 0.58)	−5.269	**<.001**	0.51 (0.34, 0.77)	−3.250	**.001**
Unknown	0.72 (0.44, 1.17)	−1.332	.183	0.62 (0.27, 1.41)	−1.137	.255
T-Stage[a]			**<.001**			**.010**
0-1	1 (Ref)			1 (Ref)		
2	1.41 (1.11, 1.78)	2.848	**.004**	1.24 (0.93, 1.65)	1.493	.135
3	1.46 (1.15, 1.85)	3.101	**.002**	1.42 (1.06, 1.91)	2.357	**.018**
4	1.80 (1.43, 2.27)	5.018	**<.001**	1.82 (1.35, 2.45)	3.954	**<.001**
N-Stage			**.005**			**<.001**
0	1 (Ref)			1 (Ref)		
1	1.19 (0.88, 1.62)	1.142	.253	1.29 (0.88, 1.90)	1.297	.195
2	1.23 (0.95, 1.58)	1.589	.112	1.61 (1.15, 2.23)	2.812	**.005**
3	1.56 (1.19, 2.06)	3.167	**.002**	1.67 (1.16, 2.39)	2.789	**.005**
Notifying institution sector			**.002**			
Private	1 (Ref)					
Public	1.35 (1.10, 1.64)	2.921	**.003**			
Rurality (SA-GCC)			.079			
Metropolitan Melbourne	1 (Ref)					
Regional Victoria	1.14 (0.99, 1.31)	1.768	.077			
IRSD Quintiles			**<.001**			**.001**
1 (Most disadvantaged)	1 (Ref)			1 (Ref)		
2	0.76 (0.62, 0.93)	-2.626	**.009**	0.82 (0.64, 1.05)	-1.571	.116
3	0.95 (0.77, 1.17)	-0.490	.624	1.05 (0.82, 1.35)	0.416	.678
4	1.03 (0.84, 1.27)	0.264	.791	1.23 (0.96, 1.59)	1.612	.107
5 (Least disadvantaged)	0.87 (0.69, 1.08)	−1.260	.208	0.85 (0.64, 1.13)	-1.095	.274
Unknown	0.33 (0.22, 0.49)	−5.371	**<.001**	0.54 (0.34, 0.86)	-2.589	**.010**
Radical treatment			**<.001**			**<.001**
No	1 (Ref)			1 (Ref)		
Yes	0.38 (0.33, 0.44)	−13.76	**<.001**	0.49 (0.41, 0.59)	-7.674	**<.001**

Bold values indicate statistical significance.
[a]T0 and T1 coalesced due to small number of T0 ($n = 3$).
[b]*P*-values in multivariate model come from the fit of the model with all 7 predictors.
Abbreviations: T, tumor; N, nodal; SA, statistical area; GCC, greater capital city; IRSD, Index of Relative Socio-economic Disadvantage.

radical treatments. The role of immunotherapy will also likely expand for these patients and trials combining it with other modalities, such as a hypofractionated radiotherapy course, may be a feasible alternative solution, allowing more patients to receive radical treatment. Cost effectiveness analyses are needed to explore the impact of these changes in practice.

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Conflict of Interest

John Reynolds is an employee of Alfred Health and reported a consulting/advisory relationship with the Australasian Leukaemia & Lymphoma Group and the Australasian Myeloma Research Consortium, research funding from Abbvie, Novartis, NHMRC, and MRFF, and ownership interests with Novartis AG and Alcon. **Susan V. Harden** reported honoraria from AstraZeneca, paid to institution for speaking at scientific meeting. The remaining authors indicated no financial relationships.

Author Contributions

Conception/design: K.W., S.S. Provision of study material or patients: R.G.S., M.B. Collection and/or assembly of data: K.W., K.K. Data analysis and interpretation: K.W., K.K., J.R., R.G.S., S.V.H., S.S. Manuscript writing: all authors. Final approval of manuscript: all authors.

Data Availability

The data underlying this article were provided by the Victorian Lung Cancer Registry and the Victorian Department of Health and Human Services by permission. Data will be shared on request to the corresponding author with permission of these 2 organizations.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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