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Prognostic Markers in Metastatic Cutaneous SCC of Head and Neck

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Abstract:

Background

The minority of head and neck cutaneous squamous cell carcinomas (HNcSCC), metastasise to regional lymph nodes. We describe the clinical outcomes and prognostic factors for node positive HNcSCC patients who underwent lymphadenectomy.

Methods

A retrospective single center study using the Kaplan–Meier method for the investigation of overall survival (OS) and loco-regional control (LRC) rate. Cox proportional hazards model was evaluated to identify prognostic factors.

Results

The median number of positive lymph nodes from149 lymphadenectomies was 2 in the neck and 1 in the parotid. The 5 years OS and LRC rates were 50% and 77%, respectively.

OS was worse among older patients (HR 1.04, P=0.015), immunosuppressed (HR 2.06, P=0.034) and patients with a high lymph nodal ratio (LNR_{tot}; calculated from the number of positive divided with the total number of nodes) (MVA; HR 1.13, P=0.019)).

Conclusions

Low LNR_{tot} is associated with improved outcomes in node positive HNcSCC.

Introduction:

Nonmelanoma skin cancer (NMSC) incidence is increasing worldwide[1], particularly in Australia[2]. Approximately 20% of cutaneous malignancies are squamous cell carcinoma (cSCC)[3]. The majority of the NMSC arise on the sun exposed head and neck region (HNcSCC). A minority of HNcSCC will metastasize to regional lymph nodes often including intraparotid lymph nodes[4-7]. In fact, HNcSCC is the most common parotid malignancy in Australia[8].

Various prognostic parameters for overall survival (OS) in patients with node positive HNcSCC have been demonstrated including the presence and extent of nodal extra capsular extension (ECE)[9-11], lymph nodal ratio (LNR) (defined as the number of positive nodes divided by the total number of nodes resected)[12], the involvement of parotid lymph nodes[3,13], differentiation of the primary tumor[14], immune-suppression[15] and margin status of the primary lesion[16,17]. However, only tumour size (T1/T2), bone invasion (T3), skeletal and perineural invasion of the skull base (T4) together with nodal size (N1/N3) and number (N2) are included in the current staging system (AJCC 7th edition staging system[18,19]). Various different staging systems have been previously proposed and investigated[8,19].

After appropriate management of the primary tumor, most patients with node positive HNcSCC will undergo neck dissection (of variable levels) with or without parotidectomy followed by adjuvant radiotherapy[20,21]. However, there remains ongoing debate regarding the recommended extent of nodal surgery (both within the neck and the parotid gland) [22].

In the current study, we describe the management and treatment outcomes of patients with node positive HNcSCC in a large skin unit at a dedicated cancer center in Australia. We investigate diverse patient, disease and treatment parameters and the association with regional control and survival outcome.

Materials and Methods:

A retrospective analysis and chart review was performed collecting demographic data, disease parameters, treatment modalities and various survival metrics for patients with node positive HNcSCC treated surgically at a single tertiary center between 1st June 2001 and 31st December 2014. The study was conducted following the approval of the local ethical committee (15/03R) according to the World Medical Association Declaration of Helsinki 2008.

Patients were identified by searching selected key words from within the electronic medical record ("skin", "cutaneous", "squamous cell carcinoma", "lymph node", "neck") Patient selection was not dependent on billing codes.

Inclusion criteria: Patients were included if they underwent lymph node dissection with curative intent for node positive HNcSCC. Patients with a history of multiple cutaneous SCC where the index lesion for the nodal disease were listed as unknown primary site.

Exclusion criteria: Patients without a history of cutaneous SCC presenting with nodal involvement were presumed to have a mucosal primary and were not included in the analysis. Patients were also excluded if essential data including pathology and operative reports were unavailable or if surgery was performed at another center. Prophylactic nodal dissection (no nodes involved), salvage surgery or surgery for radiation failure or surgery with palliative intent were not included.

Parotidectomy cases included in the data consist of superficial, total and radical parotidectomy. Neck dissection cases vary from highly selective one level dissection (e.g. level 2 together with parotid SCC), selective, modified radical and radical neck dissection. In some cases the neck levels dissected were not specifically mentioned in the operating notes, therefore, we avoid any assumption and preferred using the total number of neck and parotid nodes excised as a surrogate for extent of dissection.

We performed cox proportional hazards regression analyses of LNR_{tot} including all 149 cases. However, as the number of total nodes excised varied greatly and the lymph nodal ratio is directly influenced by the extent of dissection (denominator), calculations involving LNR were also limited to those cases where at least 10 lymph nodes were examined in the nodal specimen.

Statistics: All statistical analyses were performed in the R statistical software package using standard and validated statistical procedures. All statistical analysis results and their interpretation were independently reviewed by a statistician (AH). The overall survival (OS) and loco-regional control (LRC) rate were estimated using Kaplan–Meier method with corresponding 95% confidence intervals. Overall survival (OS) and LRC rated were calculated from the date of nodal dissection. As the specific cause of death was uknown in 40% of cases, survival calculations were limited to OS.

Univariate, multivariate Cox proportional hazards regression and post hoc models testing were used to investigate the association between OS and LRC rate with different prognostic factors.

Results:

One hundred eighty three cases of either parotidectomy, neck dissection or both were performed at the Peter MacCallum Cancer Center for HNcSCC between 1st June 2001 and 31st December 2014. 148 patients met the inclusion criteria and underwent 149 node dissections (figure 1). 24 cases were excluded due to primary tumor invasion into the parotid parenchyma with no nodal involvement. Another six cases with synchronous cutaneous and mucosal SCC were excluded. Four cases of surgery following radiation, three salvage operations for regional recurrence, two cases with insufficient data, and one palliative intent surgery were also excluded. Thirty nine patients with the appropriate key words on our search tool were operated elsewhere, therefore excluded from our cohort.

The study population is described in table 1. The median age was 78.6 years (27.5 - 95.2 years). There was a male preponderance (85.1%) and most patients had a history of an additional prior malignancy; non-melanoma skin cancer other than the index (63.1%), melanoma (9.4%) and other non-skin malignancy (23.5%). Immuno-suppression was documented in 29 patients (19.5%) mostly hematologic disease related (23 patients) and 6 patients had drug induced immuno-suppression.

The median primary skin SCC tumor diameter was 20 mm (5 - 80 mm), removed mainly from the scalp (35%), other sites of primary tumour are listed in table 1a. Most of the primary tumors were treated at early T classifications (AJCC 7th edition;T1 (46%) and T2 (49%)), and most were either moderately differentiated (45%) or poorly differentiated (49%).

The median time from primary surgery to lymph node dissection was 11.3 months (0-123 months). Overall, 79% of the patients underwent neck dissection, 21% had parotidectomy alone and 39.6% had both. The median number (and range) of positive lymph nodes dissected from the neck and parotid were 2 (1-35) and 1 (1-13), out of a total median nodal yield of 23 (1-85) in the neck and 3 (1-43) in the parotid. The median positive

maximal nodal diameter was 15 mm (2-65 mm). Using the AJCC 7th edition[18] 28% of patients had N1 disease, 70% had N2 and only 3% had N3 disease. Most (68%) of the involved nodal specimens demonstrated extra capsular extension and 52% were removed with 1 mm margins or less. The median lymph nodal ratio of the whole cohort (LNR_{tot}) was 0.2 (0.01-1). (Table 1b)

According to our institutional protocol, the majority of patients (84%) received adjuvant external beam radiation treatment (94.2% completion rate). The main reason for avoiding radiation was patient refusal (9%) followed by patients being unfit to receive adjuvant radiation (4.5%). The median radiation dose was 60 Gray (range: 20-70 Gray) delivered over a median of 30 fractions. 19 patients had radiation dose planning of less than 50 Gray due to comorbidities and/or post-operative medical status. Radiation data was incomplete for only 4 patients (2.5%). Fifteen patients (10%) had adjuvant radiation combined with chemotherapy following surgery.

With a median follow up of 37.7 months, the 2 and 5 years overall survival rates were 66% and 50% and the 2 and 5 years LRC recurrence rates were 85% and 77%, respectively (figure 2a includes the 95% CI). Most of the regional recurrences occurred during the first two years following surgery. Only six patients had regional neck recurrence three or more years following surgery. Five patients had loco-regional recurrence outside the surgical and radiation fields, in all cases this occurred within two years of treatment completion.

Univariate (UVA) and multivariate (MVA) analysis of predictors of loco-regional control are described in table 2. Younger age (HR 1.04, p=0.043) was associated with improved loco-regional control on UVA. Post operative radiation treatment (PORT) was associated with improved regional control on MVA (HR 0.17, p=0.012). Nodal classification (HR 1.57, p=0.097), number of positive lymph nodes (HR 1.03, p=0.504) and presence of ECE (HR 1.35, p=0.565) were not associated with increased rates of regional recurrence.

Patients with immune suppression as a result of lymphoproliferative disease, mainly CLL, (HR 2.06, p=0.034) and increasing diameter of primary tumour (HR 1.04, p=0.019) experienced poorer OS. Increasing age (HR 1.04, p=0.015), increasing number of positive parotid and neck nodes (HR 1.07, p=0.023) and patients with high LNR_{tot} (HR 1.13, p=0.019), were all associated with a worse OS on both UVA and MVA (Table 3). Patients undergoing PORT had a longer OS (HR 0.29, p=0.005). There was no difference in either LRC rate or OS according to whether the metastatic disease was located in the parotid, cervical nodes or both. However, the site of the primary tumor located on the auricle or behind the ear was associated with poorer OS compared to all other anatomical locations using the post hoc model analysis. There was no association between the time from primary surgery to lymph node dissection, presence of ECE, nodal maximal diameter, positive nodal margins, extent of neck dissection (according to number of total parotid or neck excised) and OS. The AJCC stage of disease was not associated with overall survival (HR 1.71, p=0.086).

Discussion:

This study presents an in-depth analysis of one of the largest single-institution experiences in the management of patients with node positive HNcSCC. The aim was to consider novel prognostic parameters to define a high risk subgroup.

Consistent with previous studies[23], most patients with HNcSCC were elderly males. Almost 20% of patients were immunocompromised, mainly due to hematological malignancies (mostly CLL) or drug induced (steroids / steroids sparing treatment) this proportion was higher than most previous study groups[24,25] and may reflect the unique referral patterns within a comprehensive cancer center. Our institutional bias as a high level tertiary referral center, together with the retrospective nature of the study explains the missing data related to the primary tumors. Both increasing age and the presence of immuno-suppression predicted for poor OS. These findings are consistent with previous publications[24].

There has been ongoing controversy about the ability of the current (7th edition) AJCC staging system to accurately predict prognosis for patients with node positive HNcSCC [23,26,27]. This controversy is reflected in the current data. There were some primary tumor features that predicted poorer prognosis (large primary skin lesion and location on the auricle and behind the ear). This is in contrast to the current AJCC staging system, where primary tumor characteristics for T1 and T2 tumors have no effect on tumor staging in patients with node positive disease. The adverse impact on survival of more advanced primary tumour characteristics in patients with node positive HNcSCC has previously demonstrated.[14,28,29] Unlike in previous studies[29] we found no association between the disease free interval and survival.

The effect of close / positive margins of the lymphadenectomy specimen on outcome is controversial as different groups have published conflicting findings arguing for same[30] or poorer OS [25,30]. The question is significant as a close / positive margin is a common

finding in the current series (52%) and in previous publications.[14,25] These rates may reflect the high incidence of parotid nodal spread (91 patients, 61.1%) and the challenge of resecting parotid nodes while preserving the facial nerve. In the current series, the lymphadenectomy close / positive margins had no prognostic effect. This may be related to the high rates of post-operative radiation therapy (PORT). Prior studies have demonstrated a correlation between maximal nodal diameter or the presence of ECE with outcomes[15,24,25], these associations were not seen in the current study.

The institutional protocol reflected in this series involves node dissection (parotidectomy and neck dissection in 61.1% and 79%, respectively) followed by PORT (84%). This protocol is accepted by most major skin cancer units[31]. Only a small portion of the current study group (10%) received adjuvant chemotherapy. In accordance with other study groups[15,21,24] PORT is associated with both OS and loco-regional rate control.

In the current series, most of the cases with low number of total nodes excised were performed together with parotidectomy for parotid metastases from cSCC - the optimal extent of lymphadenectomy for these patients remains undefined, which may explain the wide range of total nodes excised (1-85).

The prognostic significance of lymph nodal ratio has previously been described in patients with node positive mucosal SCC of the head and neck[31] .Lymph nodal ratio is an important measure as it measures both the number of positive nodes (numerator) with the number of resected nodes (denominator). LNR_{tot} was strongly associated with OS (MVA; HR 1.13, P=0.019) but not with rates of LRC. Given the range of extent of neck dissection, we repeated the LNR calculation, excluding the 27 cases with excision of less than 10 total nodes which could bias the ratio interpretation as result of a low denominator. Even without these patients, LNR remained a significant predictor of overall survival. It is difficult to explain why LNR is associated with OS and not with LRC rate. It less likely related to the extent of surgery reflected by the number of nodes excised

(denominator) which neither was associated with OS nor LRC rate. It is less likely related with adjuvant radiation which was associated with both better OS and LRC rate. However, it may be related to the number of positive nodes (numerator) which was associated with OS and not with LRC rate.

This study highlights some of the weaknesses of the current (7th edition) AJCC staging for cutaneous SCC with regard to N classification[13,19]. Whilst, this data supports the prognostic stratification of stage 3 compared to stage 4 (mostly determined by nodal staging, as only 4 patients had T4 classification) (HR=1.71, P=0.086) the stratification into N1 compared to N2 disease did not predict for either loco-regional control rate or OS (HR=1.57, P=0.097). However, it is important to note that the AJCC staging system is designed for primary staging and the majority of patients in this study had nodal disease diagnosed a median of 11.3 months following primary diagnosis (although, there was no association between the time between primary tumor and nodal excision and outcome metrics).

In conclusion, this study reflects a typical population of patients with node positive HNcSCC. Some potential important predictors of overall survival, including age and LNR may assist in better risk stratification than the factors currently included in the AJCC staging system (nodal size and number). Further studies to validate these findings are required.

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Tables legends:

Table 1:

Demographic details, primary skin index and nodal description of 149 cases

Table 2:

Uni and multi variate cox regression analyses of factors associated with loco-regional control (LRC) rate.

Table 3:

Uni and multi variate cox regression analyses of factors associated with overall survival.

Figures legends:

Figure 1:

Study scheme

Figure 2:

2a: The Overall survival (OS) and loco-regional control (LRC) rate analyses, using Kaplan-Meier method, for head and neck cutaneous SCC patients with nodal spread treated between 2001 and 2014 at Peter MacCallum cancer center. 2b: The OS stratified by various lymph nodal ratio (LNR_{tot}; calculated from the number of positive divided with the total number of lymph nodes excised of all cases).

Table 1 – Demographic details, primary skin index and nodal description of 149 cases

Demographic and primary skin index data				
Age, years	Median (range)			78.6 (27.5-95.2)
Gender	Female (percentage)			22 (14.9%)
	Male (percentage)			126 (85.1%)
Immune suppression	Number of patients (percentage) - Drug induced - Disease induced			29 (19.5%) 6 (20.7%) 23 (79.3%)
Oncological history	Non Melanoma skin ca other than the index			94 (63.1%)
	Other malignancies			35 (23.5%)
	Melanoma			14 (9.4%)
Primary index diameter, mm	Median (range)			20 (5-80)
	Unknown			81
Index site	Scalp	39 (35%)	Pre auricular	6 (5%)
	Ear	23 (21%)	Nose	6 (5%)
	Lip lower/upper	12 (11%)	Neck	2 (1.8%)
	Cheek	10 (9%)	Eye lid	1 (0.9%)
	Post auricular	10 (9%)	Chest	1 (0.9%)
Grade, differentiation	well		5 (6%)	
	moderate		37 (45%)	
	poor		40 (49%)	
	Unknown		67	
T classification AJCC staging system (7th edition)	T1	35 (46%)	T3	1 (1%)
	T2	37 (49%)	T4	3 (4%)
	Unknown		70	

Primary skin excision margins	Close/positive	27(30.3%)
	clear	62 (69.7%)
	Unknown	60
Nodal description		
Interval time T to N, months	Median (range)	11.3 (0-123.1)
	Unknown	52
Neck nodal burden, **N=117**	Median (range) number of positive nodes	2 (1-35)
	Median (range) number of total nodes	23 (1-85)
Parotid nodal burden, **N=91**	Median (range) number of positive nodes	1 (1-13)
	Median (range) number of total nodes	3 (1-43)
Parotid & neck positive nodes, N=149	Median (range)	2 (1-35)
LNR $_{tot}$ (neck & parotid), N=149	Median (range)	0.2 (0.01 – 1)
LNR (neck & parotid), N=122 (at least 10 lymph nodes excised)	Median (range)	0.16 (0.01 – 1)
Nodal margins, N=149	Positive margins (percentage)	77 (52%)
ECE, N=133	Presence ECE (percentage)	91 (68%)
Nodal maximal diameter, mm (Histological measurement)	Median (range)	15 (2-65)
	Unknown	32
N classification, N=149 AJCC staging system (7th edition)	N1 (percentage)	41 (28%)
	N2 (percentage)	104 (70%)
	N3 (percentage)	4 (3%)
Disease stage AJCC staging system (7th edition)	Stage 3	41 (28%)
	Stage 4	108 (72%)

Interval time T to N: Time between primary skin SCC excision and lymphadenectomy, **LNR**: Lymph nodal ratio, **Positive margins**≤ 1mm, **ECE:** Extra capsular extension

Table 2– Uni and multi variate cox regression analyses of factors associated with loco-regional control (LRC) rate.

Variable	n	HR [95% CI]	P-value	HR [95% CI]	P-value
		Univariate Cox regression		Multivariate Cox regression	
Age	149	1.04 [1.00, 1.09]	**0.043 ***		
Steroid immune suppression	149	3.30 [0.44, 24.90]	0.326		
Lympho- proliferative immune suppression	149	1.68 [0.56, 5.04]	0.381		
Primary index diameter	68	1.04 [1.00, 1.08]	0.096		
PORT	149	0.15 [0.06, 0.37]	**<0.001***	0.17 [0.051, 0.569]	**0.012***
T-N interval	97	1.01 [0.98, 1.03]	0.607		
Number of neck LN	149	1.04 [0.96, 1.12]	0.42		
Number positive neck LN	149	1.04 [0.96, 1.12]	0.420		
Number positive neck & parotid LN	149	1.03 [0.95, 1.12]	0.504		
LNR_{tot}	149	1.05 [0.91,1.22]	0.5		
LNR at least 10 nodes excised	122	1.06 [0.89, 1.27]	0.519		
Nodal classification	149	1.87 [0.74, 4.70]	0.176		
Disease stage	149	1.92 [0.64, 5.75]	0.218		
ECE presence	131	1.35 [0.48, 3.78]	0.565		
LN maximal diameter	117	0.96 [0.90, 1.02]	0.115		
LN positive margins	148	0.79 [0.33, 1.90]	0.592		

PORT: post-operative radiation treatment, **LN**: lymph node, **T-N interval:** time from skin lesion removal and lymphadenectomy, **LNR**: lymph nodal ratio (, Nodal and disease staging according to the AJCC staging system (7^{th} edition)**, ECE**: extra capsular extension.* Statistically significant P value

Table 3– Uni and multi variate cox regression analyses of factors associated with overall survival.

Variable	n	HR [95% CI]	P-value	HR [95% CI]	P-value
		Univariate cox regression		Multivariate cox regression	
Age	149	1.04 [1.02, 1.07]	**0.001***	1.04 [1.01, 1.08]	**0.015 ***
Steroid immune suppression	149	3.42 [1.06, 11.03]	0.082		
Lympho- proliferative immune suppression	149	2.06 [1.10, 3.85]	**0.034***		
Primary index diameter	68	1.04 [1.01, 1.07]	**0.019***		
PORT	149	0.32 [0.17, 0.59]	**0.001***	0.29 [0.131, 0.643]	**0.005 ***
T-N interval	97	1.01 [0.99, 1.02]	**0.409**		
Number of neck LN	149	1 [0.98, 1.01]	0.65		
positive neck LN	149	1.06 [1.01, 1.10]	**0.039***		
Number positive neck & parotid LN	149	1.06 [1.02, 1.10]	**0.026 ***	1.07 [1.02, 1.13]	**0.023 ***
LNR_{tot}	149	1.15 [1.05, 1.25]	**0.004***	1.13 [1.03, 1.24]	**0.019***
LNR at least 10 nodes excised	122	1.13 [1.02, 1.25]	**0.022***		
Nodal classification	149	1.57 [0.92, 2.68]	0.097		
Disease stage	149	1.71 [0.90, 3.26]	0.086		
ECE Presence	131	1.06 [0.58, 1.93]	0.842		
LN maximal diameter	117	0.99 [0.97, 1.03]	0.737		
LN positive margins	148	1.11 [0.65, 1.90]	0.691		

PORT: post-operative radiation treatment, **LN**: lymph node, **T-N interval:** time from skin lesion removal and lymphadenectomy, **LNR**: lymph nodal ratio, Nodal and disease staging according to the AJCC staging system (7^{th} edition)**, ECE**: extra capsular extension. * Statistically significant P value

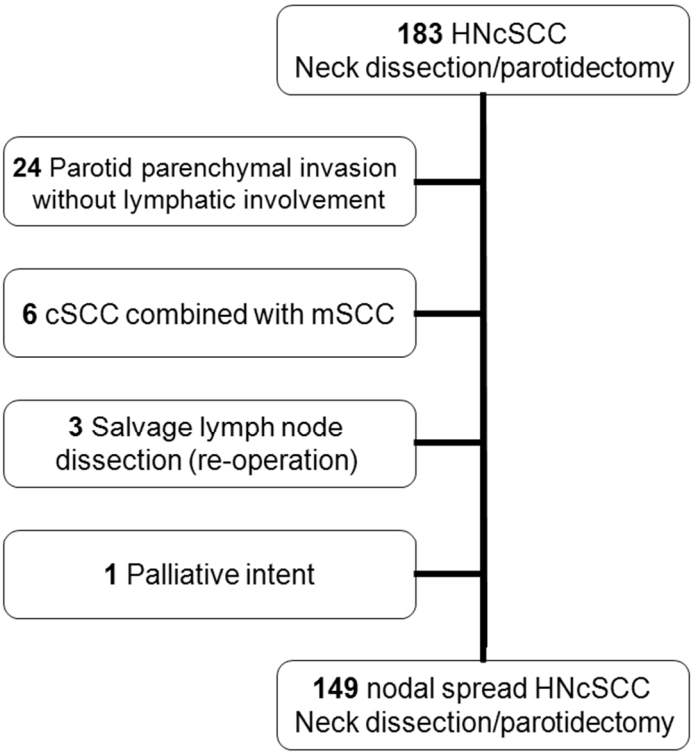

Figure 1
Study scheme
254x190mm (96 x 96 DPI)

Figure 2a

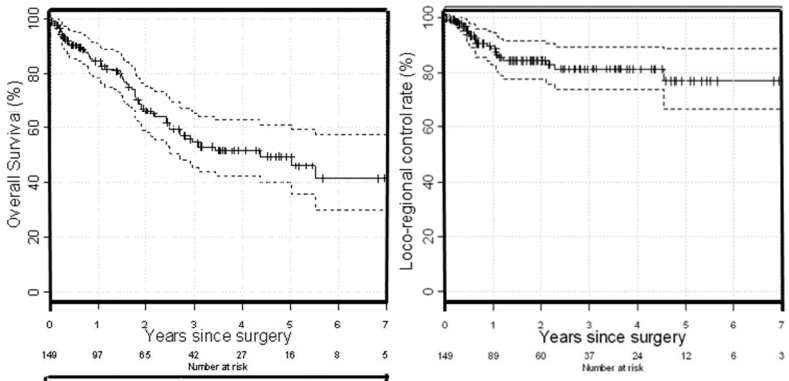

Figure 2b

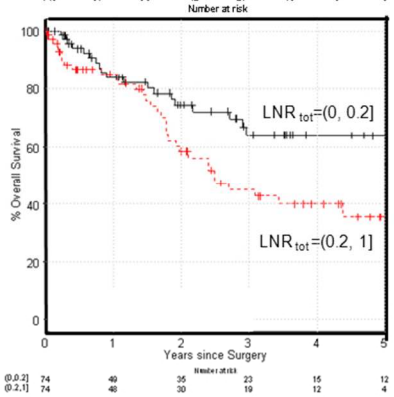

Figure 2
2a: The Overall survival (OS)
254x190mm (96 x 96 DPI)