

## SYSTEMATIC REVIEW

### **Risks and Benefits of Central Neck Dissection (CND) in Differentiated Thyroid Carcinoma (DTC)**

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#### **Abstract**

**Introduction:** *The role of central neck dissection (CND) remains controversial in differentiated thyroid cancer (DTC). Risk and benefit of CND is necessary to be identified for judging whether CND will be performed or not.*

**Methods:** *A literature search was performed in MEDLINE (pubmed) using main keywords such as differentiated thyroid carcinoma (DTC), central neck dissection (CND), total thyroidectomy. The literature had inclusion criteria english language literature with risk and benefit of CND. We used qualitative approach to summary descriptive papers result.*

**Results:** *Sixteen trials were analyzed. There was no increased risk of recurrent laryngeal nerve (RLN) injury (temporary or permanent), permanent hypocalcemia, or locoregional recurrence when CND was performed in addition to TT. Postoperative temporary hypocalcemia was more common after TT with CND than after TT alone.*

**Conclusion:** *TT alone results in less surgical morbidity in the immediate postoperative period and an identical locoregional recurrence rate compared with TT plus CND.*

**Key words:** *differentiated thyroid carcinoma, central neck dissection, total thyroidectomy*

## **Risiko dan Manfaat *Central Neck Dissection (CND)* pada *Differentiated Thyroid Cancer (DTC)***

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### **Abstrak**

**Latar Belakang:** Peran *central neck dissection (CND)* masih kontroversial pada *differentiated thyroid cancer (DTC)*. Risiko dan manfaat *CND* penting diketahui untuk pertimbangan melakukan *CND*.

**Metode:** Dilakukan pencarian penelitian yang dipublikasikan di MEDLINE (pubmed) menggunakan kata kunci *differentiated thyroid carcinoma (DTC)*, *central neck dissection (CND)*, *total thyroidectomy*. Penelitian yang diambil memiliki kriteria inklusi, penelitian dengan bahasa inggris dengan risiko dan manfaat *CND*. Kemudian dilakukan analisis sistematik dengan pendekatan kualitatif untuk merangkum hasil penelitian yang bersifat deskriptif.

**Hasil:** Analisis yang dilakukan pada 16 penelitian tidak terjadi peningkatan risiko cedera *Recurrent laryngeus nerve (RLN)* yang terdiri dari cedera sementara dan cedera permanen atau terjadi kekambuhan lokal regional yang dilakukan pada *CND* setelah *TT*. Kejadian hipokalsemia sementara pasca operasi lebih umum terjadi pada *TT* dengan *CND* dibandingkan dengan *TT* sendiri.

**Simpulan:** Tiroidektomi total sendiri morbiditasnya lebih kecil pada periode pasca operasi dan memiliki kekambuhan lokal dan regional hampir sama dibandingkan *TT* dengan *CND*.

*TT* disertai *CND* memiliki manfaat menurunkan angka rekurensi. Namun *TT* disertai *CND* memiliki risiko terjadinya hipokalsemia sementara dan cedera *RLN* sementara yang lebih besar dibandingkan *TT* saja.

**Kata kunci:** *differentiated thyroid carcinoma*, *central neck dissection*, tiroidektomi total

## Introduction

Differentiated thyroid carcinoma (DTC) is a case of thyroid malignancies which is mostly frequent to be detected, covering 90% of the new cases of thyroid malignancies in the areas provided with sufficient iodine in the world. This kind of tumor largely appears to be slow growing tumor and normally has good prognosis with survival rate for 10 years reaching 90%. Nevertheless, DTC, particularly papillary thyroid carcinoma (PTC) frequently metastasizes into regional lymph gland. Metastasis of lymph gland is found in 20-50% of PTC patients and micro metastasis is identified in 90% of the patients. Central compartment is the most frequent location of metastasis of lymph gland, with the prevalence of metastasis ranges between 30 to 90%. Metastasis of regional lymph gland is associated with the increase of recurrence rate (30%). The increasing recurrence rate causes morbidity and mortality to increase.<sup>1,2</sup>

The implementation procedures of DTC should cover regional lymph gland management including central compartment lymph gland inside. Central neck dissection (CND) as one way to obtain adequate regional control seems to be controversial.

The different risks and benefits in different healthcare centre encourage debates on CND roles.<sup>3</sup> CND itself can be in form of prophylactic CND (pCND) or therapeutic CND (tCND). The difference of both lays on the identification of central compartment lymph gland status. If the status of central compartment lymph gland has been identified, then CND performed is therapeutic.<sup>4</sup> In this systematic review, the discussion is on pCND.

Thyroidectomy is the gold standard procedure to obtain adequate local control. Meanwhile, to obtain regional control, there are several action alternatives in form of CND or radioiodine ablation (RIA).<sup>5,6,7,8</sup> Surgeons selecting CND argued that CND had benefits to decrease recurrence and decline morbidity due to recurrent operation. Meanwhile, the surgeons who are not selecting CND argued that only with total thyroidectomy (TT) can give the same benefit with CND with lower complication risk.<sup>9,10</sup>

Benefit of CND in DTC is to prevent recurrence so that it can minimize morbidity. The risk of CND complication is associated with the increase of hypocalcemia due to hypoparathyroidism

and recurrent laryngeus nerve (RLN) injury compared to only total thyroidectomy.<sup>6</sup> In relation to various data regarding the risks and benefits of CND in different healthcare centre, data analysis qualitatively needs to be performed from different research to obtain a comprehensive overview concerning the risks and benefits of CND related to recurrence and complication.<sup>11,12</sup>

## Methods

Data collection strategy is performed based on electronic database (Medline, ScienceDirect-Elsevier, Springerlink and Embase) from January 1995 to April 2015 to identify all research investigating CND for DTC case. The data collection/searching strategy employs terms *differentiated thyroid carcinoma, total thyroidectomy, central node dissection*. Relevant articles were collected and employed to expand the reference materials to use. Furthermore, systematic analysis was performed by using qualitative approach to summarize the research results in form of descriptive research.

## Results

This systematic review identified 3.558 subjects from 16 studies published between

January 1995 and April 2010. Of 1.499 subjects (42%) underwent TT with CND and 2.059 subjects (58%) only underwent TT. The heterogeneity of research and patients were identified. The majority of research was *trial retrospective* or cohort and there was only one research with *randomized control trials* (RCT). (Table 1) Afterwards, research classification was done based on the topics to analyze, such as temporary hypocalcaemia, permanent hypocalcaemia, temporary and permanent recurrences laryngeal nerve (RLN) injury, local and regional recurrence, central and non-central recurrence, post operative recurrence of tCND and pCND.

## Surgery Morbidity

Of 11 studies mentioning the data of postoperative temporary hypocalcaemia after the performance of TT with CND compared to temporary hypocalcaemia in only TT. Of 13 studies reported the prevalence of permanent hypocalcaemia. The definition of temporary and permanent hypocalcaemia ranges from subjective symptom in the results of laboratory examination. The overall prevalence of temporary hypocalcaemia after the performance of TT with CND is significantly higher than TT itself which is

262/845 (31%) compared to 239/1478, (16%). (Table 2). In relation to permanent hypocalcaemia, there is not difference between TT with CND and TT itself 17/1096 (1.6%) compared to 22/1696 (1.3%). (Table 3).

Of 10 research recorded the prevalence of temporary RLN injury after the performance of TT with CND or only TT. Meanwhile, 11 research elaborated the prevalence of permanent RLN injury. Not similar to the definition of hypocalcaemia, the diagnosis of RLN injury is made consistently, characterized by unilateral or bilateral vocal chord disfunction seen by direct laryngoscope. The prevalence of temporary RLN injury after the performance of TT with CND tends to be slightly higher than only TT which is 17/1096 (1.6%) compared to 22/1696 (1.3%). (Table 4). The prevalence of permanent RLN injury after the performance of TT with CND is similar to permanent RLN injury after the performance of only TT which is 15/918 (1.6%) compared to 19/1423(1.3%). This results show that there is no significant difference between the use of TT with CND and only TT in regard to permanent or temporary RLN injury. (Table 5)

### **Local and regional recurrence**

Post-operative local and regional recurrence in DTC was evaluated in 12 studies. The definition of local and regional recurrence is not consistent in surgical literature. The most of surgeons agreed that the increase of *thyroglobulin* or antibody level *antithyroglobulin* or positive imaging with USG, CT axsial or radioiodine scan to overall body indicate recurrence and will be confirmed by pathology during post-operation. As described previously, firstly we collect each recurrence after TT therapy with CND and compare it with the result of only TT. We found that the prevalence of local and regional recurrence was higher after only performance of TT compared to after the performance of TT with CND which was 119/1520 (7.8%) compared to 71/1050 (6.8%). (Table 6)

We conducted analysis on subgroup with recurrence in various locations in each lateral, central and multifocal recurrence research. After the selection, it was found 10 research of recurrence in central neck after the performance of TT with CND and only TT, based on analysis on subgroup and the prevalence of recurrence. The prevalence of recurrence in central neck is similar in each group. In the group performing TT with

CND was obtained 14/805 (1.7%) compared to only TT 30/1288 (2.3%). (Table 7 and 8).

### **Discussion**

The role of CND in thyroidectomy for DTC case is still controversial.<sup>13</sup> Index to measure the accuracy in evaluating the different benefits from CND procedures for DTC is by central compartment metastasis and has been proved to prevent metastasis LNS in DTC and has benefit to increase survival rate<sup>14</sup> In relation to DTC characteristic which is slow growing tumor, it is hard to evaluate the accurate data regarding long term survival. Mortality due to other causes during observation period about the significant role of CND in improving survival in DTC has not been evaluated.<sup>15</sup> In the future, long term research with the aim to evaluate survival, evaluate morbidity and mortality and disease-free period in comparing the effectiveness and implementation of each surgical procedure is necessary.

### **Surgical Morbidity**

This systematical review revealed higher level of temporary hypocalcaemia prevalence in patients undergoing TT with CND compared to only performance of TT.<sup>16</sup> This risk is deemed to be caused by

wide dissection from central compartment which can interfere blood supply to parathyroid gland, particularly ipsilateral side gland. Moreover, TT with incidental parathyroidectomy or without transplantation of simultaneous parathyroid gland can also cause the prevalence of post-operative hypocalcaemia to more frequently occur.<sup>16,17</sup> The prevalence of temporary vocal cord disorder is higher in the performance of TT with CND. It can occur due to mild injury from RLN because of surgical manipulation procedures, local edema or small-scale hematoma.<sup>18</sup>

Total Thyroidectomy still causes permanent hypocalcaemia of 1-2% and recurrent permanent neural injury in larynx which is external branch of nervus laryngeus superior, although the surgery is performed by experienced surgeons.<sup>19,20</sup> The results of our analysis are consistent in observation in DTC patients which is 1.3% undergoes hypocalcaemia and 1.34% undergoes RLN injury after the only performance of TT. The morbidity of permanent surgery does not increase in the patients with TT procedures accompanied with CND. Therefore, the addition of CND cannot improve the rate of permanent complication risk.

However, in this systematic review, not all studies have similarity in defining the criteria of hypocalcaemia, both quantity point and time cut off. Several studies employ the criteria of hypocalcaemia if the score of blood calcium is smaller than 2,0 mg/ml, whereas others use the criteria less than 2,15 mg/ml.<sup>21</sup> Meanwhile, 1 research uses period limitation of 1 year to determine whether the subject undergoes permanent hypocalcaemia, which other studies employ 6 month period.<sup>6</sup> Heterogeneity of this hypocalcaemia criteria can bias to the research about hypocalcaemia in CND.

### **Recurrence**

Recurrence normally occurs in tumor with bigger size, older patients, male patients, invasive-growing tumor is identified from both lymphovascular and extracapsular extension and proven to have metastasis of lymph gland and high risk in the prognostic evaluation.<sup>22,23</sup> Indicator between positive correlation between central compartment lymph gland and bad prognosis still raise debates. In other words, the risk factors may be able to predict positive score of metastasis of central compartment lymph gland and affect post-operative mortality due to mortality in DTC case are final point which is hard to be used for the surgeons

more focus on local and regional recurrence and the evaluation on significant intervention for the patients, although traditionally it can be accepted that metastasis of cervical lymph gland is associated with local and regional recurrence.<sup>21</sup>

Only performance of total thyroidectomy give similar success to disease control compared to TT with tCND or pCND. A study conducted by Cranshaw stated that local and regional recurrence in PTC patients with micro metastasis of lymph gland is equal to PTC patients without metastasis.<sup>25,26</sup> It can be concluded that the benefits of CND to reduce locoregional recurrence are possibly estimated too high. The main rationale to regularly perform pCND is to prevent recurrence and risks of neural injury and permanent hypoparathyroid in tCND. However, in several studies, data is found that tCND does not increase morbidity.<sup>27,28</sup>

*American Association Thyroid (ATA)* has guidelines which have been revised for DTC case in November 2009 regarding thyroid tumor <sup>29</sup> The recommendation correlates between surgical strategy and local and regional lymph gland involvement. This

committee is more careful in CND issue and recommends prophylactic CND in patients with high increase of T3 and T4. This recommendation can only achieve ranking with C level meaning that it is recommended based on the notion of experts, but the committee acknowledges that prophylactic dissection is a controversial issue to date.<sup>30</sup> Therefore, the recommendation for this case is clearly required as long as there is surgeon to handle it. On valid strategy recommended is performing only thyroidectomy and recurrent operation is undertaken in recurrence case performed in small group which can be eventually developed the detection method of metastasis of lymph gland so that it can avoid unnecessary morbidity in the patients largely.<sup>31,32</sup>

Of 1 research reported that post-operative RAI therapy in the group of subject undergoing TT and CND.<sup>15</sup> Meanwhile, other 11 studies reported post-operative RAI therapy only.<sup>26</sup> This can be bias in evaluating the difference between higher detection level of metastasis of lymph gland in pCND and relatively lower recurrence after the performance of thyroidectomy without CND. Specified data about the proportion of patients in different group receiving RAI therapy and patients with RAI

therapy undergoing lymph gland recurrence is not obtained, so that we cannot perform analysis in this systematic review. Other limitation from this systematic review is that most of research reports taken are retrospective cohort, so that the level of data accuracy is not as high as prospective research.

### Conclusion

TT with CND has benefits to reduce recurrence rate. However, TT with CND has greater risks of temporary hypocalcaemia and temporary RLN injury compared to only TT. Research about the risks and benefits of CND using the same criteria of CND complication and RAI therapy is required.

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Tabel 1. Characteristics of Research

Data Source	Village in	Sample capacity in each group	Additional dissection in lateral disease	Postoperative / Radioiodine therapy	Follow-up period	Stadium
Henry et al., 1998	RT	1: TT (50) 2: TT+PCND (50)	1: 00 LND 2: 00 LND	Not described	12	3b, level B
Steinmuller et al., 1999	RT	1: TT+CND (53) 2: TT+LND (15) 3: TT (70)	1: 00 LND 2: 15 LNDs 3: 00 LND	Not described	72	4, level C
Wade et al., 2003	RT	1: TT+TCND+TLND (24) 2A: TT+PCND+PLND (185) 2B: TT+PCND (50)	1: 24 MRNDs 2A: 185MRNDs 2B: 0 MRND	Not described	>53	3b, level B
Gemsenjager et al., 2003	ICS	1: TT+TCND (42) 2: TT + PCND (29) 3: TT (88)	45 LNDs overall	Ablation I131 (69) overall	97.2	2b, level B
Sywak et al., 2006	ICS	1: TT+ICND (55) 2: TT (391)	1: 0 MRND 2: 0 MRND	Regularly performed	>24.5	2b, level B
Roh et al., 2007	RCT	1: TT+BCND (82) (TT +TCND (42) (TT +PCND (40) 2: TT (73)	1: 26 LNDs 2: 00 LND	Regularly performed	Not described	2b, level B
Palestini et al., 2008	RT	1: TT+BCND (64) 2: TT+ICND (93) 3: TT (148)	1: 33 LNDs 2: 00 LND 3: 00 LND	Not described	Not described	3b, level B
Davidson et al., 2008	RT	1: TT+TCND (19) 2: TT+TLND (73) 3: TT+TCND+TLND 14	73 LNDs overall	Regularly performed	78	3b, level B
Perrino et al., 2009	ICS	1: TT+PCND (92) 2: TT (159)	35 LNDs overall	140 Ablation I131 overall	69.2	2b, level B
Zuniga et al., 2009	ICS	1: TT+PCND (136) 2: TT (130)	None	1: 79 I terapi I131 2: 55 terapi I131	82.8	2b, level B
Besic et al., 2009	ICS	1: TT +TCND or PCND (30) 2: TT (224)	55 LNDs overall	124 Ablation I131 overall	56	2b, level B
Rosenbaum et al., 2009	RT	1: TT+TCND (22) 2: TT (88)	1: 7 MRNDs 2: 6 MRNDs	1: 18 Ablation I131 2: 56 ablasI I131	>33.6	3b, level B
Roh et al., 2009	RCT	1: TT+CND (148) 2: TT (49)	1: 36 LNDs 2: 00 LND	Regularly performed	36	1b, level A
Sadowski et al., 2009	RT	1: TT+BCND (168) 2: TT+ICND (11) 3: TT (130)	1: 33MRNDs 2: 00 MRND 3: 00 MRND	209 Ablation I131 overall	38.8	3b, level B
Shen et al., 2010	RT	1A:TT+TCND+TLND (81) 1B: TT+TCND (110) 2: TT (191)	1A: 81 LNDs 1B: 0 LND 2: 0 LND	Not described	>24	3b, level B
Moo et al., 2010	RT	1: TT+PCND (45) 2: TT (36)	None	1: 32 Ablation I131 2: 24 Ablation I131	37.2	3b, level B

RT: retrospective trial; ICS: individual cohort study; RCT: randomized controlled trial; TT: total thyroidectomy; CND: central neck dissection; LND: lateral neck dissection; TCND: therapeutic CND; PCND: prophylactic CND; BCND: bilateral CND; ICND: ipsilateral CND; TLND: therapeutic LND; MRND: modified radical neck dissection

Table 2. Temporary Hypocalcaemia

Research or subgroup	TT + CND			TT		
	n	Total	%	n	Total	%
Henry et al., 1998	7	50	14.0%	4	50	8.0%
Steinmuller et al., 1999	21	53	39.6%	25	70	35.7%
Sywak et al., 2006	10	56	17.8%	32	391	8.2%
Roh et al., 2007	25	82	30.4%	7	73	9.6%
Palestini et al., 2008	45	157	28.6%	19	147	12.9%
Perrino et al., 2009	8	92	8.6%	11	159	6.9%
Besic et al., 2009	13	30	43.3%	57	224	25.4%
Rosenbaum et al., 2009	19	22	86.3%	51	88	57.9%
Roh et al., 2009	58	148	39.1%	10	49	20.4%
Moo et al., 2010	14	45	31.1%	2	36	5.5%
T.Shen et al., 2010	42	110	38.1%	21	191	10.2%
Total	262	845	31.0%	239	1478	16.0%

Table 3. Permanent Hypocalcaemia

Research or subgroup	TT + CND			TT		
	n	Total	%	N	Total	%
Henry et al., 1998	2	50	4.0%	0	50	0%
Steinmuller et al., 1999	1	53	1.9%	0	70	0%
Gemsenjager et al., 2003	1	71	1.4%	0	88	0%
Sywak et al., 2006	1	56	1.8%	2	391	0.5%
Roh et al., 2007	4	82	4.8%	1	73	1.3%
Palestini et al., 2008	0	157	0%	4	147	2.7%
Perrino et al., 2009	1	92	1.1%	6	159	3.8%
Besic et al., 2009	2	30	6.6%	6	224	2.7%
Rosenbaaum et al., 2009	1	22	4.5%	0	88	0%
Sadowski et al., 2009	0	180	0%	0	130	0%
Roh et al., 2009	4	148	2.7%	1	49	2%
Moo et al., 2010	0	45	0%	2	36	5.5%
T.Shen et al., 2010	0	110	0%	0	191	0%
Total	17	1096	1.6%	22	1696	1.3%

Table 4. Temporary RLN Injury

Research or subgroup	TT + CND			TT		
	n	Total	%	n	Total	%
Henry et al., 1998	2	50	4.0%	3	50	6.0%
Steinmuller et al., 1999	2	53	3.7%	6	66	9.1%
Sywak et al., 2006	1	56	1.8%	4	391	1.0%
Roh et al., 2007	6	82	7.3%	3	73	4.1%
Palestini et al., 2008	10	157	6.3%	2	147	1.4%
Perrino et al., 2009	2	92	2.1%	5	159	3.1%
Rosenbaaum et al., 2009	2	22	9.0%	2	88	2.3%
Sadowski et al., 2009	15	180	8.3%	6	130	4.6%
Moo et al., 2010	2	45	4.4%	0	36	0%
T.Shen et al., 2010	2	110	1.8%	7	191	3.7%
Total	17	1096	1.6%	22	1696	1.3%

Table 5. Permanent RLN Injury

Research or subgroup	TT + CND			TT		
	n	Total	%	n	Total	%
Henry et al., 1998	0	50	0%	0	50	0%
Steinmuller et al., 1999	1	53	1.9%	0	70	0%
Sywak et al., 2006	0	56	0%	4	391	1.0%
Gemsenjager et al., .2003	4	71	5.6%	0	88	0%
Roh et al., 2007	3	82	3.7%	2	73	2.7%
Palestini et al., 2008	0	157	0%	2	147	1.4%
Perrino et al., 2009	1	92	1.1%	4	159	2.5%
Rosenbaaum et al., 2009	2	22	9.1%	2	88	2.3%
Sadowski et al., 2009	4	180	2.2%	4	130	3.1%
Moo et al., 2010	0	45	0%	0	36	0%
T.Shen et al., 2010	2	110	1.8%	2	191	1.0%
Total	15	918	1.6%	19	1423	1.3%

Table 6. Local and regional recurrence

Research or subgroup	TT + CND			TT		
	n	Total	%	n	Total	%
Gemsenjager et al., .2003	6	71	8.5%	2	88	2.3%
Wada et al., 2003	5	259	1.9%	1	155	0.6%
Sywak et al., 2006	2	56	3.6%	22	391	5.6%
Roh et al., 2007	1	82	1.2%	3	73	4.1%
Davidson et al., 2008	5	19	26%	22	77	29%
Perrino et al., 2009	5	92	5.4%	22	159	14%
Rosenbaaum et al., 2009	1	22	4.5%	2	88	2.3%
Zuniga et al., 2009	19	136	14%	26	130	20%
Roh et al., 2009	1	148	2.1%	0	49	0%
Besic et al., 2009	0	10	0%	2	83	2.4%
Moo et al., 2010	2	45	4.4%	6	36	17%
T.Shen et al., 2010	24	110	22%	11	191	5.8%
Total	71	1050	6.8%	119	1520	7.8%

Table 7. Central recurrence

Research or subgroup	TT + CND			TT		
	n	Total	%	n	Total	%
Gemsenjager et al., .2003	4	71	5.6%	0	88	0%
Wada et al., 2003	5	259	1.9%	1	155	0.6%
Sywak et al., 2006	0	56	0%	7	391	1.8%
Roh et al., 2007	1	82	1.2%	3	73	4.1%
Davidson et al., 2008	5	19	26.3%	22	77	29%
Perrino et al., 2009	0	92	0%	5	159	3.1%
Rosenbaaum et al., 2009	0	22	0%	2	88	2.3%
Zuniga et al., 2009	19	136	14%	26	130	20%
Roh et al., 2009	0	148	0%	0	49	0%
Sadowski et al., 2009	0	169	0%	4	130	3.1%
Besic et al., 2009	0	10	0%	1	83	1.2%
Moo et al., 2010	0	45	0%	2	36	5.6%
T.Shen et al., 2010	0	110	0%	6	191	3.1%
Total	14	805	1.7%	30	1288	2.3%

Table 8. Non-central recurrence

Research or subgroup	TT + CND			TT		
	n	Total	%	n	Total	%
Gemsenjager et al., .2003	2	71	2.8%	2	88	2.3%
Sywak et al., 2006	2	56	3.6%	17	391	4.3%
Roh et al., 2007	1	82	1.2%	2	73	2.7%
Perrino et al., 2009	5	92	5.4%	17	159	10.7%
Rosenbaaum et al., 2009	1	22	4.5%	0	88	0%
Roh et al., 2009	1	148	0.7%	0	49	0%
Besic et al., 2009	0	10	0%	1	83	1.2%
Moo et al., 2010	2	45	4.4%	4	36	11.1%
T.Shen et al., 2010	15	110	13.6%	5	191	2.6%
Total	29	636	4.6%	48	1158	4.1%