Suspected Cancer:

recognition and management of suspected cancer in children, young people and adults

Update of clinical guideline 27

Appendix J3:

Sections from NICE clinical guideline 27 health economics and example search strategy that have been removed

Appendix C

THE HEALTH ECONOMICS OF REFERRAL FOR SUSPECTED COLORECTAL CANCER

Introduction

Symptoms and signs that may signify an underlying cancer are frequently of benign origin and are widely prevalent in the general population, thus leading to difficulty in diagnosis in primary care settings. The guideline recommendations aim to facilitate appropriate referral of patients suspected of having cancer, and attempt to define clinical circumstances with a reasonably high chance of finding an underlying cancer. Equally, it is hoped that the guidelines will help professionals identify patients who are unlikely to have cancer and who may be observed in a primary care setting or who may require non-urgent referral to a hospital. This will avoid inappropriate or excessive investigations that may have psychological or physical ill effects and will consume more resources

Methodology

The analysis that follows is based on published data and expert opinion. However, due to the limited evidence, we have made particular use of the research findings of the guideline group's specialist advisor on colorectal cancer to estimate the prevalence of cancers and symptoms by age group (Thompson M et al, 2003{952}, supplemented by additional details provided by MR Thompson).

We wished to examine the implications of three options for urgent referral of patients with suspected colorectal cancer. The three options vary depending on which signs and symptoms are considered for urgent referral. The single symptoms considered in these models are: change in bowel habit and rectal bleeding. The signs include anemia, abdominal mass and rectal mass. The different symptom combination groups are based on the recommendations made by the guideline group.

The measure of effectiveness in each of the options is the number of patients with cancer referred urgently (seen by a specialist within two weeks) after visiting the primary care professional or 'early' referred patients. The costs include not only the cost at the primary care level but also the cost of the diagnostic test at the secondary level. Since colonoscopy is the 'gold standard' test , we assumed it was performed in all referred patients. We also assumed that colonoscopy has a 100% sensitivity for detecting cancer (Lewis, 2004{953}).

The model is based on a hypothetical cohort of 10,000 symptomatic patients presenting to primary care professionals with rectal bleeding or change in bowel habit. The prevalence of cancer in this cohort is assumed to be .0602 (Thompson et al 2003); in other words 602 of the 10,000 people with symptoms in the cohort have cancer. The strategies compared are described in the next section and are taken from the guideline recommendations and possible variations.

Referral Strategies

Referral Strategy A: This strategy involves urgent referral on the basis of a combination of symptoms (according to PPV of these combinations) without considering signs. Patients that are not urgently referred are assumed to be followed up on a 'treat wait and watch

option' for three months. Column I in
table1[1] presents all the possible symptom combinations considered in strategy A;
these were mainly derived from the recommendations made by the guideline group. Column II defines the referral decision based also on the recommendations by the guideline group, 1 = refer, 0=do not refer, instead treat watch and wait. Column III presents the distribution of the cohort within the group (i.e. the proportion of patients with the symptoms) and column IV the positive predictive value of each symptom combination (the information of these two columns was derived mainly from Thompson 2003 {952}).

Referral Strategy B: This referral strategy considers not only symptom combinations but also the presenting signs. In this strategy we assume that identifying these signs will require diagnostic examinations and tests in the primary care setting, in particular, rectal digital examination to detect any rectal mass, examination to detect palpable abdominal mass and a full blood count (FBC) to detect anemia. The decision rules interpreted from the recommendations by the group and the proportion of patients and cancers in each group are presented in table 3. All those patients who presented any sign were assigned a 1 (refer urgently) in the decision rule. This is in accordance with the guideline group's recommendations that any patient with a rectal or abdominal mass and/or iron deficiency anemia of below 10 gms/dl should be referred urgently.

Referral Strategy C: This strategy is less selective and considers the alternative of urgently referring all patients that present to the primary care professional with any sign or symptom potentially related to colorectal cancer (universal referral). This strategy is straightforward and implies the urgent referral to colonoscopy of all the 10 000 symptomatic patients in the cohort.

Specific Effect (clinical) Implications of Strategies

Strategy A: Table 2 considers the implications of the decision rules assumed (table1) in strategy A. In this strategy 4,693 people (of the 10 000 total population presenting to the professionals) without cancer are not referred and placed in the
'treat, watch and wait' alternative. However, 72 of the 602 (12%) patients with cancer are not referred urgently. Table 2 also shows that 38% of the cancers in the age group from 40 to 60 are not referred urgently, while in the age group< 40 none of the cancers presented are referred urgently.

Strategy B: This strategy assumes that the primary care professional performs a full blood count (FBC) and a rectal digital examination (RDE) in all symptomatic patients presenting with rectal bleeding or change in bowel habit. With this strategy (Table 4) 561 (93%) of the 602 patients with cancer are urgently referred; only 7% of the patients with cancers are delayed in this referral strategy. However, the number of patients referred without cancer is slightly higher than with strategy A (100 more persons without cancer referred). At first sight this may seem surprising. However, Table 2 shows that in order to urgently refer 30 more patients with cancers, making strategies A and B "equally" efficient, it would be necessary to change the decision rule of strategy A to referral of the 60 and over age group that present bleeding with no change in bowel habit plus perianal symptoms. This group is the one that presents the highest predictive value when the decision rule was not to refer urgently. This would lead to the referral of 1,064 more patients, of whom only 32 would have cancer (see sensitivity analysis below).

Strategy C: The clinical results of this strategy are straightforward. It implies urgent referral of 100% of patients with cancer (approximately 602). However, approximately 93% of patients who are referred would not have cancer.

[1] Tables in this paper are presented without decimals, this cause that sometimes percentages do not exactly to 100 or to some minimum apparent inconsistency with the operations.

Costs implications of Strategies

Unit costs used and costs implications for the different strategies are given in Table 5-6. All costs variables are in UK pounds for the year 2003. The main sources of these costs are the National Reference Costs 2003 and the Personal Service Research Unit (PSRU) Unit cost of Health Care and Social Care 2003.

For strategy A it is assumed that an FBC is only performed on referred patients. The total cost of this strategy is £1,225,990. To estimate the cost of strategy B an FBC is assumed for all the 10,000 symptomatic patients in the cohort. We assume that rectal digital examination (RDE) does not represent an additional cost above the cost of consulting the primary care professional. The total cost of strategy B is £1,301,837.

In strategy C we consider two alternatives: performing FBC among all the 10,000 patients (since all were referred) or performing the test among only 50% of the patients (an assumption that probably more closely reflects current practice). The first one gives a cost of £2,159,867 while the second of £2,104,933.

Results

In Table 6 we present the main cost-effectiveness results when strategies are compared. In graph 1 the Incremental cost effectiveness ratio of the alternatives is presented. Strategy B shows an incremental cost effectiveness ratio of
£2,446.6 per extra early detected (urgently referred) cancer patient when compared with strategy A. This seems good value for money, bearing in mind that the cost of screening for colorectal cancer under the Nottingham trial
protocol was £5,290 per cancer detected (at 2002 prices) and the announcement in 2002 by the Ministry of Health that screening for colorectal cancer will be rolled out nationally.When we compare strategy C with strategy B, the incremental cost effectiveness ratio for each extra early diagnosed case increases to £20,927. This alternative implies early diagnose of all symptomatic patients with cancer but the extra cost per diagnosed case is quite high compared with alternative B. Also this alternative will imply extra costs if the potential complications of colonoscopy are taken into account. Furthermore, universal referral of symptomatic patients as urgent cases for colonoscopy will increase waiting times overall.

The results of modelling strategy B showed that simple diagnostic actions in primary care such as FBC and rectal examination have the potential to increase the positive predictive value of a strategy based on symptoms combination. Strategy B, therefore, appears to be a cost effective alternative. The recommendations made by the guideline group consider both signs and symptom combinations and reflect strategy B.

Sensitivity Analysis

A series of one-way sensitivity analyses of the model were undertaken. These involved varying parameters in turn to assess how sensitive the model was to changes in variables such as costs or effectiveness.

Table 7 shows how the results change if we want to increase the effectiveness of strategy A. To increase the number of patients with cancer referred urgently, the decision rule has been changed to include referral of people 60 and over with bleeding and no change in bowel habit and perianal symptoms. With this change
32 more cancer cases are now referred urgently. Compared with strategy B, this option increases effectiveness in only .69 cancer cases at an extra cost of
£132,723.

Table 8 shows how results change if the effectiveness of strategy B is altered, the decision rule to include of the group with the highest positive predictive value among the groups of patients

not referred (aged 60 and presenting with bleeding, with no change in bowel habit (+perianal symptoms) and without signs). With this strategy, 576 out of the 602 cancers are referred urgently. In order to achieve this level of effectiveness, 6,379 patients are referred. Compared with strategy A this strategy presents an incremental cost effectiveness ratio of £5,682 per cancer case referred urgently. This strategy might be considered if there were sufficient specialists and colonoscopists available. Strategy C compared with strategy B involves incremental cost effectiveness of £26,249 per referred cancer case.

Table 9 shows how results change if the effectiveness of strategy B is improved at the minimum cost. The decision rule has been changed so that the minimum number of patients have to be referred and including groups in which more than 1 cancer cases are found. This leads to inclusion of the group aged 40 to 60 with bleeding with no change in bowel habit, no perianal symptoms and no signs. In this group there are 355 persons, 5 having cancer. With this strategy, 6,379 cases are urgently referred of which 566 are cancers. Compared with strategy A this strategy presents an incremental cost effectiveness ratio of £3,924 per early cancer referred case. Strategy C compared with this version of strategy B presents incremental cost effectiveness £22, 057 per early referred cancer case.

If performing rectal examination doubles the normal amount of time general practitioners spend with patients (and therefore increases the consultation costs), the incremental cost effectiveness ratio of strategy B increases in comparison with strategy A to £8,836. This strategy assumes the unit cost of a general practitioner consultation is £40. However, a doubling of consultation time is probably an overestimate, and a rectal examination would be preformed in high proportion of patients in any strategy.

Future research and Discussion

In this study we have only partially evaluated the strategies; to evaluate in full the costs and consequences of the different strategies would require consideration of the clinical path that patients in the 'treat wait and watch' group follow. This would require data on the effectiveness of this option, and questions such as the following would have to be answered:

- Of the patients that have cancer that are placed on 'treat, watch and wait', how many are referred after a three month observation period, and would any difference be expected in this number between strategy A and B?
- Of the patients without cancer that are placed in the 'treat, watch and wait' group, how many recover and how many are referred with suspected cancer, and is there any difference expected in these numbers between strategy A and B?

Further research could also explore the implications for costs of the probability of perforation or bleeding is a small proportion of cases undergoing colonoscopy. Research is also required to determine the benefits if any of investigating low risk symptomatic patients in comparison to the 'treat, watch and wait' strategy. These patients might be considered as candidates for a screening programme (whenever it is introduced) as they still have a higher probability of having malignancy than asymptomatic patients (Lewis 2004). Future research of the effects of changing the age thresholds would also be helpful.

Tables and Diagrams

Table 1. Assumptions in strategy A. Decision rules and population % used in alternative A.

i	ii	iii	iv
Combinations of symptoms by age	**decision rule 1=urgently referred, 0=do not**	**distribution of symptomatic patients***	**Positive predictive value***
60 and over			
Bleeding + change in bowel habit (+ or - ps)	1	0.1623	0.1702
bleeding with no change in bowel habit(+ps) bleeding with no change in	0	0.1064	0.0300
	1	0.0599	0.1159
	1	0.1779	0.0682
40-60			
Bleeding + change in bowel habit(+or-ps) bleeding with no change in bowel habit(+ps) bleeding with no	1	0.1234	0.0512
	0	0.1331	0.0104
	0	0.0361	0.0211
<40		0.0659	0.0221
Bleeding +change in bowel habit(+or-ps) bleeding with no change in bowel habit(+ps) bleeding with no change in	0	0.0396	0.0053
	0	0.0684	0.0000
Total		**1**	

*Data derived from Thompson M, 2003.

+ps = with perianal symptoms

-ps = without perianal symptoms

Table 2. Consequences of strategy A.

Combinations of symptoms by age	decision rule 1=refer urgently, 0= do	no. of persons with symptoms	number of persons with cancer	Positive predictive value (PPV)	no. of persons urgently referred (according to decision	no. of patients with cancer urgently referred	no. of patients without cancer urgent	no. of persons with cancer not referred	avoided referrals of patients without
60 and over									
bleeding+change in bowel habit(+or-ps) bleeding with no change in bowel habit(+ps)	1	1,623	276	0.1702	1,623	276	1,347	0	0
	0	1,064	32	0.0300	0	0	0	32	1,032
	1	599	69	0.1159	599	69	529	0	0
	1	1,779	121	0.0682	1,779	121	1,658	0	0
40-60							0		0
bleeding+change in bowel habit(+or-ps) bleeding with no change in bowel habit(+ps)	1	1,234	63	0.0512	1,234	63	1,171	0	0
	0	1,331	14	0.0104	0	0	0	14	1,317
	0	361	8	0.0211	0	0	0	8	354
<40		659	15	0.0221	0	0	0	15	644
bleeding+change in bowel habit(+or-ps) bleeding with no change in bowel habit(+ps)	0	396	2	0.0053	0	0	0	2	394
	0	684	0	0.0000	0	0	0	0	684
Total		10,000	602		5,235	530	4,705	72	4,693

ps= perianal symptoms

Table 3 Main assumptions of strategy B. Referral decision rule and proportion of patients by

Combinations of symptoms by age	Person presenting signs	Referral decision rule, 1=	Proportion of symptomatic patients*	Proportion of persons with cancer*	Positive predictive value*
60 and over					
Bleeding +change in bowel habit (+ or – ps) Bleeding +change in bowel habit (+ or – ps) bleeding with no change in bowel habit (-ps) bleeding with no change in bowel habit (-ps) bleeding with no	ye	1	0.0168	0.1694	0.607438017
	s	1	0.1455	0.2892	0.119694802
	no	1	0.0038	0.0323	0.509090909
	ye	1	0.0561	0.0829	0.089108911
	s	1	0.0046	0.0276	0.358208955
	no	0	0.1018	0.0253	0.014996592
		1	0.0131	0.0956	0.439153439
40-60	ye	1	0.1648	0.1060	0.038720539
Bleeding + change in bowel habit (+ or – ps) Bleeding +change in bowel habit (+ or – ps) bleeding with no change in bowel habit (-ps) bleeding with no change in bowel habit (-ps) bleeding with no	s				
	no	1	0.0052	0.0311	0.36
	ye	1	0.1182	0.0737	0.037558685
	s	1	0.0006	0.0046	0.444444444
	no	0	0.0355	0.0081	0.013671875
		1	0.0026	0.0069	0.157894737
<40	ye	0	0.1304	0.0161	
Bleeding +change in bowel habit (+ or – ps) Bleeding +change in bowel habit (+ or – ps) bleeding with no change in bowel habit (-ps) bleeding with no change in bowel habit (-ps) bleeding with no change in bowel habit (+ps)	s	1	0.0024	0.0092	
	no	0	0.0635	0.0150	
	ye	1	0.0012	0.0012	
	s	0	0.0384	0.0023	
	no	1	0.0001	0.0000	
	ye	0	0.0164	0.0000	
	s	1	0.0006	0.0000	
Total			1	1	

group.

ps= perianal symptoms

Table 4. Consequences of strategy B. Note: totals might not add exactly given that numbers are presented without decimals.

	signs	decision rule1=refer urgently	no. of person with symptoms	number of persons with	Positive predictive value (PPV)	no. of person urgent	no. of patients with cancer	no. of patients without cancer	no. of persons with cancer	avoided referrals
60 and over										
bleeding+change in bowel habit (+ or – ps)	yes	1	168	102	0.6074	168	102	66	0	0
bleeding+change in bowel habit (+ or – ps)	no	1	1,455	174	0.1197	1,455	174	1,281	0	0
bleeding with no change in bowel habit(-ps)	yes	1	38	19	0.5091	38	19	19	0	0
bleeding with no change in bowel habit(-ps)	no	1	561	50	0.0891	561	50	511	0	0
40-60										
bleeding+change in bowel habit (+ or – ps)	yes	1	46	17	0.3582	46	17	30	0	0
bleeding+change in bowel habit (+ or – ps)	no	0	1,018	15	0.0150	0	0	0	15	1,002
bleeding with no change in bowel habit(-ps)	yes	1	131	58	0.4392	131	58	74	0	0
bleeding with no change in bowel habit(-ps)	no	1	1,648	64	0.0387	1,648	64	1,584	0	0
<40										
bleeding+change in bowel habit (+ or – ps)	yes	1	52	19	0.3600	52	19	33	0	0
bleeding+change in bowel habit (+ or – ps)	no	1	1,182	44	0.0376	1,182	44	1,138	0	0
bleeding with no change in bowel habit(-ps)	yes	1	6	3	0.4444	6	3	3	0	0
bleeding with no change in bowel habit(-ps)	no	0	355	5	0.0137	0	0	0	5	350
bleeding+change in bowel habit (+ or – ps)	yes	1	26	4	0.1579	26	4	22	0	0
bleeding+change in bowel habit (+ or – ps)	no	0	1,304	10	0.0074	0	0	0	10	1,294
bleeding with no change in bowel habit(-ps)	yes	1	24	6	0.2353	24	6	18	0	0
bleeding with no change in bowel habit(-ps)	no	0	635	9	0.0142	0	0	0	9	626
Total		10,000	602			5,362	561	4,801	41	4,597

ps= perianal symptoms

Table 5. Cost implications of different strategies

	unit cost (£)	strategy A	strategy B	strategy C i	ii
urgently referred patients		**5,235**	**5,362**	**10,000**	
Costs of patients referred					
GP visit[1]	£20	£104,700	£107,240	£200,000	£200,000
Nurse time[2]	£7.66	£40,135	£41,109	£76,667	£38,333
FBC	£3.32	£17,380	£17,802	£33,200	£16,600
colonoscopy	£185	£968,475	£991,970	£1,850,000	£1,850,000
sub-total		£1,130,690	£1,158,121	£2,159,867	£2,104,933
no patients do not referred		**4,765**	**4,638**	**0**	**0**
Costs					
GP visit	£20	£95,300	£92,760		
Nurse time	£7.66	0	£35,558		
FBC	£3.32	0	£15,398		
sub total		£95,300	£143,716	0	0
Total Costs per strategy		£1,225,990	£1,301,837	£2,159,867	£2,104,933

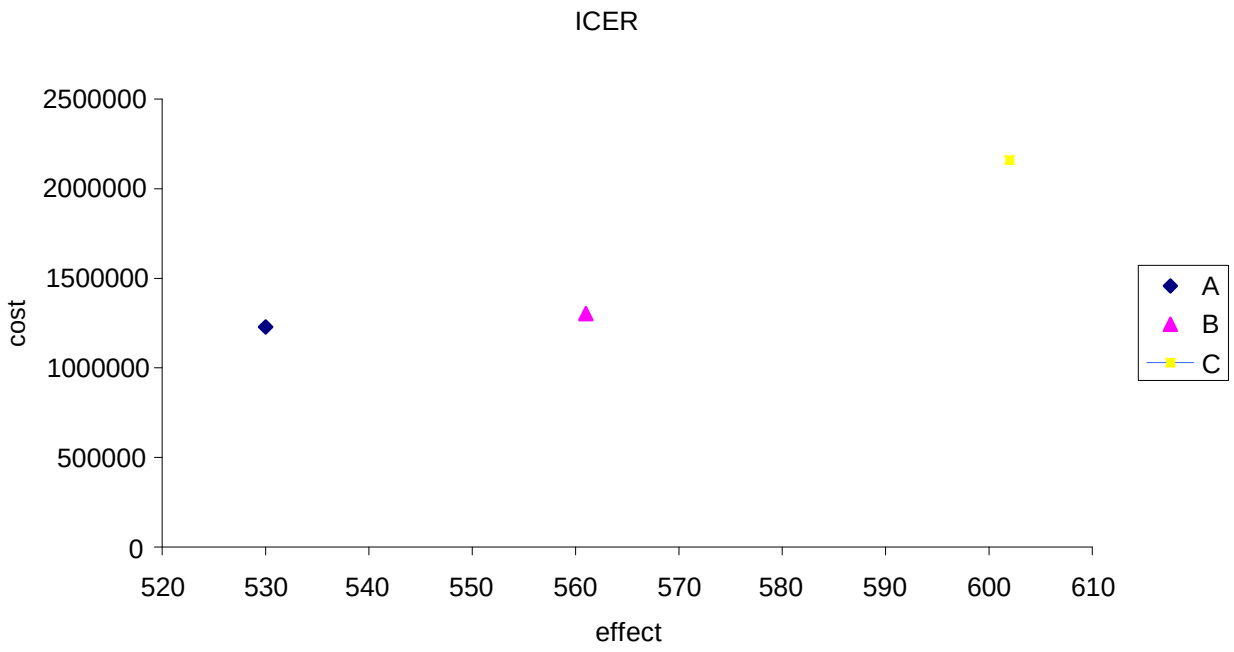
1.per consultation lasting 9.3 minutes
2. Consultation of 10 minutes

Table 6 Comparison of costs and consequences

	Strategy A	Strategy B	Strategy C
costs	£1,225,990	£1,301,837	£2,159,867
effectiveness	530	561	602
average cost effectiveness	£2313.18	£2320.56	£3587.818
incremental effectiveness		31	41
incremental costs		£75,846	£858,030
incremental cost effectiveness		£2,446.66	£20,927.56*

*Compared with strategy B

Figure 1. Incremental Cost Effectiveness Ratio



Sensitivity Analysis

Table 7. Changing decision rule of strategy A. Comparison of strategy A and B

	Strategy B	**Strategy A**
numbers referred	5361.78	6298.99
cancers early referred	561.22	561.91
costs	£1,301,795.21	£1,434,518.86
effectiveness	561.22	561.91
average cost effectiveness	£2319.58	£2552.91
incremental effectiveness		0.69
incremental costs		£132,723.64
incremental cost effectiveness		£191,321.13

Table 8. Changing decision rule of strategy B (next group with highest ppv)

	Strategy A	**Strategy B**	**Strategy C**
numbers referred	5,235	6,379	10,000
cancers early referred	530	576	602
costs	£1,225,956	£1,490,068	£2,159,867
effectiveness	530	576	602
average cost effectiveness	£2,313	£2,585	£3,588
incremental effectiveness		46	26
incremental costs		£264,112	£669,799
incremental cost effectiveness		£5,682	£26,249

Table 9. Changing decision rule of strategy B (increase cancer early detection at minimum cost)

	Strategy A	Strategy B	Strategy C
numbers referred	5,235	5,717	10,000
cancers early referred	530	566	602
costs	£1,225,956	£1,367,505	£2,159,867
effectiveness	530	566	602
average cost effectiveness	£2,313	£2,416	£3,588
incremental effectiveness		36	36
incremental costs		£141,549	£792,362
incremental cost effectiveness		£3,924	£22,057

Table 10. Strategy B costs double for RDE of strategy B.

	Strategy A	Strategy B	Strategy C
numbers referred	5,235	5,362	10,000
cancers early referred	530	561	602
costs	£1,225,956	£1,501,795	£2,159,867
effectiveness	530	561	602
average cost effectiveness	£2,313	£2,676	£3,588
incremental effectiveness		31	41
incremental costs		£275,839	£658,071
incremental cost effectiveness		£8,836	£16,137

Bibliography

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James D Lewis, Alphonso Brown, Rusell Localio and Sandford Schwartz, Initial evaluation of rectal bleeding in young persons: a cost effectiveness analysis. Ann of Inter Med. 2002

Appendix D

An example search strategy

Head & Neck Cancer - signs & symptoms

Ovid MEDLINE Search Strategy:
---

1 exp "Sensitivity and Specificity"/ (166652)
2 false negative reactions/ or false positive reactions/ (23559)
3 (sensitivity or specificity or accura$).ti,ab. (538688)
4 diagnos$.ti,ab. (833681)
5 predictive value$.ti,ab. (29516)
6 reference value$.ti,ab. (5658)
7 ROC.ti,ab. (5161)
8 (likelihood adj ratio$1).ti,ab. (2582)
9 monitoring.tw. (138051)
10 (false adj (negative$1 or positive$1)).ti,ab. (30151)
11 (randomized controlled trial or controlled clinical trial).pt. (255624)
12 double blind method/ or single blind method/ (87265)
13 practice guideline.pt. (8298)
14 consensus development conference$.pt. (4307)
15 review.pt. (1058397)
16 review.ab. (236076)
17 (meta-analysis or metaanalysis).ab. (7932)
18 meta-analysis.pt. (9542)
19 meta-analysis.ti. (5002)
20 (cohort adj stud$).ti,ab. (19677)
21 cohort studies/ (50729)
22 (single blind$3 or double blind$3 or triple blind$3).ti,ab. (74311)
23 or/1-22 (2730007)
24 exp Head/ and Neck neoplasms/ (1249)
25 ((oro-pharyn$ or hypopharyn$ or cranio-pharyn$ or acoustic) adj2 (tumor$ or tumour$ or neoplas$ or cancer$ or carcinoma$)).tw. (2140)
26 (((head and neck) or head & neck) adj2 (tumor$ or tumour$ or neoplas$ or cancer$ or carcinoma$)).tw. (14284)
27 (((ear nose and throat) or ear nose & throat or ENT) adj2 (tumor$ or tumour$ or neoplas$ or cancer$ or carcinoma$)).tw. (284)
28 ((mouth$ or tooth or teeth or dental) adj2 (tumor$ or tumour$ or neoplas$ or cancer$ or carcinoma$)).ti,ab. (1438)
29 (thyroid$ adj2 (tumor$ or tumour$ or neoplas$ or cancer$ or carcinoma$)).tw. (17591)

30 ((tongue$ or ear$ or lip$ or eye$) adj2 (tumor$ or tumour$ or neoplas$ or cancer$ or carcinoma$)).tw. (28920)
31 exp Nervous system neoplasms/ (106092)
32 ((brain or cerebr$ or mening$ or crani$) and (tumor$ or tumour$ or neoplas$ or cancer$ or carcinoma$)).tw. (53912)
33 ((CNS or central nervous system) and (tumor$ or tumour$ or neoplas$ or cancer$ or carcinoma$)).tw. (10798)
34 glioma$.ti,ab. (18169)
35 or/24-34 (198215)
36 (weight loss or cachexia).tw. (24858)
37 ((loss adj2 appetite) or anorex$).tw. (14779)
38 (tired$ or astheni$ or fatig$).tw. (29467)
39 malaise.tw. (3025)
40 headache.tw. (24073)
41 (seizure$ or fit$ or convulsion$).tw. (135615)
42 balance disturbance.tw. (55)
43 hearing loss.tw. (15097)
44 deaf$.tw. (17706)
45 tinnit$.tw. (3488)
46 earache.tw. (154)
47 (dizzy or dizziness or vertigo).tw. (10744)
49 (intellectual impairment or (personality adj2 change$)).tw. (1986)
50 urinary incontinen$.tw. (7698)
51 (monopare$ or hemipare$).tw. (5017)
52 acalculi$.tw. (100)
53 (confused or confusion or confusional state$).tw. (17645)
54 ((recogni$ adj3 face$) or facial recognition).tw. (1428)
55 ((contralateral sensory or contralateral or sensory) adj (loss or neglect)).tw. (1406)
56 agraphaesthe$.tw. (1)
57 (neglect adj2 opposite limb$).tw. (0)
58 hallucinat$.tw. (5039)
59 (memeory disturb$ or amnesi$ or (memory adj2 loss) or (deja vu or dejavu)).tw. (7573)
60 ((Broca$ or expressive or anterior) adj aphasia).tw. (312)
61 ((Wernicke$ or receptive or posterior) adj aphasia).tw. (179)
62 ((nominal or anomic or amnestic) adj aphasia).tw. (71)
63 ((global or central) adj aphasia).tw. (156)
64 anosmia.tw. (802)
65 (visual field defect$ or visual loss or visual disturbance$ or scotoma or flashes).tw. (10870)
67 (aniscoria or miosis or pupillary constriction).tw. (1063)
68 pupillary dilatation.tw. (200)
69 ophtalmoplegi$.tw. (44)
70 loss of sweating.tw. (35)
71 (ptosis or sensory loss$).tw. (4705)
72 (jaw deviation or neuralgia or trigeminal or facial pain or facial weak$ or facial palsy or facial spasm$).tw. (17851)
73 myokymia.tw. (336)
74 dribbl$.tw. (253)
75 ((cornea$ or eye$) adj2 ulceration$).tw. (662)
76 (loss of taste or hyperacu$ or (abnormalit$ adj gaze) or diplopi$ or squint or amblyopi$).tw. (9207)

77 (enophtalm$ or dysarthri$ or agraph$ or acquired dyslexia or ataxi$ or

(aprax$ adj 2 gait) or dressing aprax$ or constructional apraxia).tw. (17226)
78 (monoplegi$ or hemipare$ or hemipleg$ or parapare$ or tetrapare or vomit$).tw. (37859)
79 (dyssynerg$ or tremor$ or chorea or dyston$ or hemiballism$ or athetos$ or diadochokine$).tw. (19161)
80 (titubat$ or hypoton$ or bradykine$ or akine$).tw. (14164)
81 or/36-80 (422501)
82 exp primary health care/ (37776)
83 (primary care or primary health care).tw (34407)
84 Family Practice/ (42868)
85 Physicians, Family/ (9178)
86 (family practi$ or family doctor$ or family physician$ or gp$ or general practi$ or nurs$).tw. (298509)
87 or/82-86 (359916)
88 4 and 35 and 81 and 87 (64)
89 animal/ (3680245)
90 human/ (8604397)
91 89 not (89 and 90) (2826035)
92 88 not 91 (64)
93 letter.pt. (512455)
94 comment.pt. (256817)
95 editorial.pt. (164978)
96 or/93-95 (709834)
97 92 not 96 (64)
98 limit 97 to English language (49)