Abstract

Thyroid cancer is a complex disease requiring management by a large multidisciplinary team. The number of patients with a diagnosis of thyroid cancer is significantly increasing year on year, and traditional models of consultant led follow up are no longer sustainable. Although nurse led cancer follow up clinics are becomining increasingly common, thyroid cancer nurse led follow up clinics are rare. An excellent understanding of the disease, treatment and management of risk of disease recurrence is essential for safe patient care, and is discussed in this article. The clinic discussed utilises the skill set of head and neck nurse specialists, including psychological support, coping strategies for long term side effects of treatment and non-medical prescribing. A patient survey of the service revealed high levels of patient satisfaction and a desire to continue face to face consultations rather than telephone clinics.

Key words: Thyroid cancer, nurse led clinic, stratification, patient satisfactrion, cancer risk

Background - Thyroid cancer

The last thirty years have seen a rapid increase in the numbers of patients diagnosed with thyroid cancer – currently around 3500 cases per year (Cancer Research UK, 2017). *See Figure 1.* Thyroid cancer is a very rare disease and accounts for less than 1% of all cancers. However the incidence of thyroid cancer in the UK has increased by 155% since the early 1990s (Cancer Research UK, 2015). In 2015, 3528 new cases of thyroid cancer were diagnosed in the UK: thyroid cancer affects predominantly young women, 35-39 years, and there appears to be little, if any, impact from deprivation rates on the incidence of thyroid cancer (Cancer Research UK, 2015).

Patients typically present with a painless lump at the root of the neck that gradually increases in size. Other symptoms can include:

- a hoarse voice that doesn't have an obvious reason: the recurrent laryngeal nerve can become damaged as a result of cancer invasion which causes a hoarse voice
- difficulty swallowing: tumour compression of the oesophagus
- difficulty breathing: tumour compression of the trachea
- pain in the front of the neck

and less commonly:

- flushing of the face: elevation of calcitonin in medullary thyroid carcinoma
- frequent loose stools or diarrhoea because elevation of calcitonin in medullary thyroid carcinoma

The British Thyroid Association (BTA) *Guidelines for the Management of Thyroid Cancer* (BTA, 2014) are closelt followed by multidisciplinary teams (MDTs) treating patients with thyroid cancer and treatment includes surgery to remove the thyroid gland (total thyroidectomy) with removal of any suspicious or metastatic lymph nodes in the neck (see Illustration 2). In some cases a hemi-thyroidectomy may be sufficient when the cancer is small (less than 1cm) *(see Figure 3).* Radioactive iodine (radioiodine) is commonly given following surgery in patients who have papillary thyroid cancer; however in medullary thyroid cancers radioiodine is not considered as medullary cancers are

not sensitive to radioiodine. In some patients, external beam radiotherapy is given for patients considered to be at high risk of cancer recurrence.

Treatment of thyroid cancer is complex and involves a large MDT at specialised treatment centres. There are four types of thyroid cancer; medullary, papillary, follicular, and anaplastic. Less than 1% of all thyroid cancers are anaplastic (Cancer Research UK, 2015): it usually affects elderly patients who often present via A&E with sudden onset respiratory stridor. Papillary and follicular are often grouped together as differentiated thyroid cancer (DTC). Diagnosis is achieved with ultrasound guided fine needle for cytology and / or diagnostic hemi-thyroidectomy. Medullary thyroid cancer is treated surgically as it is radio-iodine refractive. Thyroid cancer can metastasise via the lymphatic system and a lymph node clearance of the front of the neck is sometimes undertaken at the time of surgery. If there is any suspicion or confirmation that other nodes in the neck are affected a neck dissection is also performed. Post-operative radiotherapy may be used for medullary if there is thought to be a high risk of recurrence or incomplete excision, but this treatment modality is rare. Approximately 20-25% of patients in this medullary group have a genetic pre-disposition to its development. Differentiated thyroid cancer (DTC) is the most common type of thyroid cancer (90%). It can be treated by a combination of surgery and radio-iodine.

Patients are risk stratified at two key stages (BTA, 2014):

- Following surgery using histopathology results and radiology and TNM staging (T= primary tumour size; N= number of affected lymph nodes; M= whether distant metastasis has occurred). The decision to offer further treatment is based on these results

- At 9-12 months following radio-iodine treatment.

Risk stratification helps the MDT to understand treatment pathways, patient prognosis and follow-up pathways.

Follow up

Current national guidelines state that thyroid cancer has a long natural history where late recurrences occur but can be treated successfully with a view to cure or long term survival (BTA, 2014). This has placed an increasing burden on consultant teams which follow-up patients for life as is currently recommended following treatment. Long term, multi-disciplinary consultant led follow-up is recommended practice as thyroid cancer is known to recur many years after treatment in 5-23% of patients (Mitchell et al, 2016).

Murchie et al (2016) investigated cancer survivors preferences to inform new models of follow-up care and found that patients from a number of different cancer sub-sites and found that respondents appeared willing to accept follow-up by a specialist nurse, trainee specialist doctor or GP provided that they were compensated by other changes in their follow-up, notably greater continuity of care. This mirrors the views of health professionals who are increasingly recognising the benefits of nurse-led cancer follow up (Wells, Semple & Lane, 2015).

Macmillan Cancer Support's Recovery Package and NHS Improvement highlight the potential benefits of risk-stratifying follow up of cancer patients (Macmillan Cancer Support, 2015; NHS Improvement, 2016). National policy in the UK from both the Government and Macmillan Cancer Support articulates the need for change from the traditional one size fits all consultant led follow up

model, to models that are patient centred and holistic (Department of Health et al, 2010). An ambitious strategy was launched by the Independent Cancer Taskforce (Cancer Research UK, 2015) which aimed to transform cancer care between 2015 and 2020 including alternative models of follow up following cancer treatment. Individual care plans may range from discharge and self-care, to monitoring by a specialist nurse or AHP, or continued consultant follow up and monitoring. The British Thyroid Association (BTA) also supports alternative models of follow up such as nurse led clinics (BTA, 2014).

Consensus exists amongst the medical profession for follow-up of thyroid cancer patients to detect recurrence and second primaries (Simo *et al*, 2016). However, as the population ages and more patients are surviving cancer, traditional models of consultant led follow up are unsustainable. Although it is assumed that consultant led follow up is the safest way to detect recurrence and second primaries, there is evidence that nurses can safely follow up cancer patients (Moore et al, 2002). Additionally, nurse-led follow-up has been found to have a positive effect on a patient's quality of life (de Leeuw et al, 2012) and patient satisfaction remains high over time (Berglund et al 2015). A systematic literature review (Lewis et al 2009) found that continuity of care and unhurried consultations are of major importance to patients – something that the thyroid nurse led clinic is able to provide.

The clinic at the Royal Preston Hospital was established in 2013 as a result of a challenge by a consultant ENT Surgeon, who felt that the clinical nurse specialist (CNS) team could significantly improve the experience of thyroid cancer patients by providing a nurse led clinic for low risk patients. A consultant-led clinic runs alongside the nurse-led clinic. Therefore, if the CNS requires a consultant review of a patient with thyroid cancer a second clinic attendance is not required on a separate day. The clinic was established a full year ahead of national guidelines by the BTA. The clinic is focused on minimising the risk of recurrent disease using medical management of thyroid stimulating hormone (TSH) suppression. The production of thyroxine from the thyroid gland has vital roles in digestion, heart and muscle function. It is regulated by a constant 'feedback' loop. The hypothalamus secretes thyrotropin-releasing hormone (TSR) which in turn stimulates the pituitary gland to produce TSH. When the levels of thyroxine increase the production of TSR and TSH is reduced and thereby regulating the level of thyroid hormones in the body (Tortora and Derrickson, 2017). It is this mechanism that is used to manage the risk of disease recurrence: by managing the dose of levothyroxine (the pharmacological form of thyroxine) the TSH is surpressed so that it doesn't stimulate growth of any thyroid cells (which could potentially be cancerous).

As patients are followed up for life, there is the opportunity for strong therapeutic relationships to develop between CNS and patient. For example, in addition to managing the risk of cancer recurrence in this way, the CNS has the opportunity to explore quality of life issues directly impacted by physiological levels of thyroxine. The potential effect on health status (including fatigue) and mood in patients taking TSH-suppressive doses of levothyroxine is well recognised (Samuels *et al,* 2014). Additonally, the CNS appointments are longer than their medical counterparts which gives time for discussing strategies for managing fatigue which is extremely common following treatment, however there are few evidence based management strategies in post-treatment fatigue management (To *et al*, 2015).

Historically, thyroid cancer patients who were in long term follow up would never see the same doctor twice (due to the Specialist Registrar rotation), and so at every appointment would have to repeat his/her clinical history which was frustrating and by its very nature could not facilitate the development of a therapeutic relationship over time. A sound understanding of thyroid cancer and its management, including the risk of disease recurrence, is essential in order to safely manage the risk of disease recurrence.

The BTA has key recommendations for follow-up (British Thyroid Association, 2014) which utilise the common skillset of a Head and Neck Clinical Nurse Specialist (CNS) (Webber, 2008), however, the recommendation includes clinical examination of the neck. United Kingdom national multidisciplinary guidelines for the management of thyroid cancer also state that clinical examination of the neck must be performed as part of routine follow up (Mitchell et al, 2016). Clinical palpation and assessment of neck lumps is not a skill commonly adopted by head and neck CNSs. However, at the author's Trust a Rapid Access Neck Lump Clinic was established in 2003 which is, in part, CNS led. Appropriate clinical examination skills were taught to the CNS team and, following rigorous assessment by a senior consultant the assessment of necks skill set was signed off as competent. This created an ideal opportunity for nurse led follow up of thyroid cancer patients that provided the traditional medical skill set necessary to conform to national guidelines but also the holistic assessment and support embedded within the CNS role.

A pro-forma was developed by the team which ensured that all the key clinical information is collected and reviewed at every appointment (see illustration). Ultrasound request rights were secured for the three CNS's running the clinic.

Guidelines on frequency of follow-up were developed and agreed at the local Thyroid NSSG (Network Site Specific Group) which are more stringent than the BTA guidelines (6 monthly for 2 years rather than 1 year, then annually thereafter).

Before attending the clinic a patient has a surveillance ultrasound scan and routine bloods including Thyroid Function Tests and Thyroglobulin (non-stimulated). The test results, recent clinical history and clinical assessment are then analysed and a plan agreed with the patient. The plan aims to minimise the risk of cancer recurrence by suppressing the Thyroid Secretory Hormone (TSH) between 03-2.0mIU/L using Levothyroxine as stated in the BTA guidelines. In addition, support for patients to manage the long term side effects from treatment is discussed with the patient.

However, by introducing a pro-forma based assessment tool the opportunity for practising different standards of care from one health professional to another reduces significantly. A patient experience survey showed patients value the therapeutic relationship which began at diagnosis and then continues throughout treatment and follow up.

The follow up clinic has diagnosed only one episode of recurrence during its existence: this suggests that the model of risk stratification and follow-up is fit for purpose (see case study). However, as risk of recurrence is life long and the clinic has only been in existence for six years further cases of recurrence are not unexpected.

Survey Design

A simple seven-question anonymous patient satisfaction questionnaire was developed by the

authors using Survey Monkey software. The questionnaire collected both quantitative and qualitative data to allow the patients the opportunity to give feedback in free text. Ethical approval was not required as this was an audit of the service.

Patient population

The study population included all patients attending the clinic and predominantly females under the age of 50 years which reflected the age and sex distribution of patients at diagnosis.

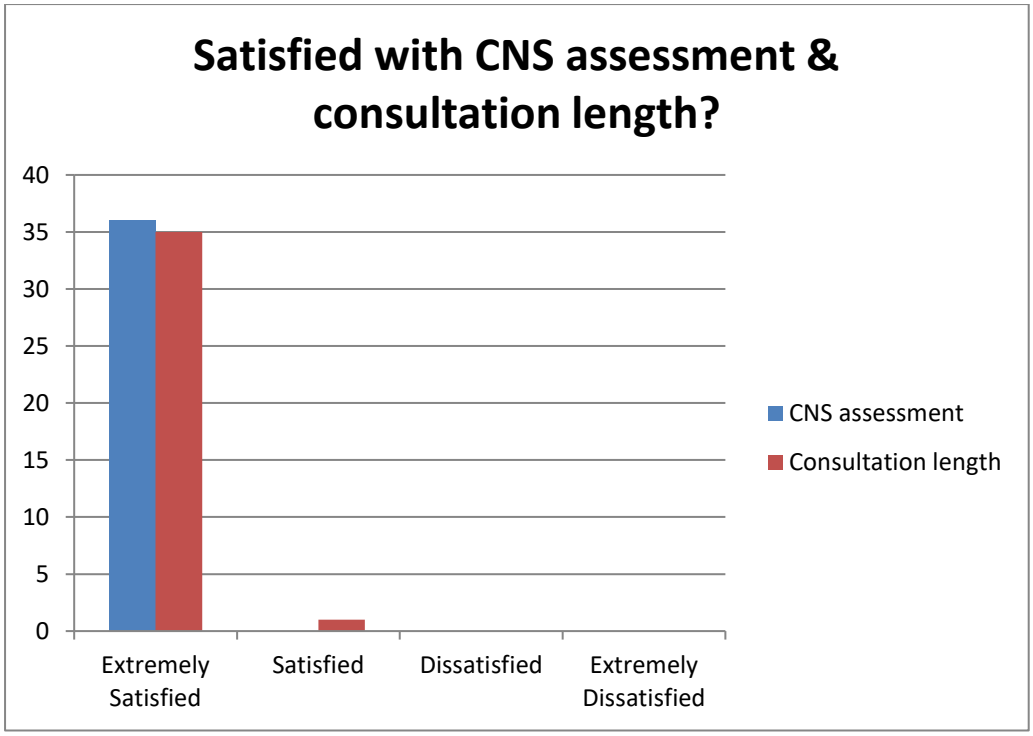
Data collection

Over a six week period during Spring 2019, all patients attending clinic were offered the opportunity to complete the feedback questionnaire. All 36 patients agreed to take part. Following the patients' consulation in clinic, questionnaires were completed electronically on Survey Monkey using an electronic tablet: privacy was given to the patient whilst completing and submitting the survey. 36 complete responses were obtained.

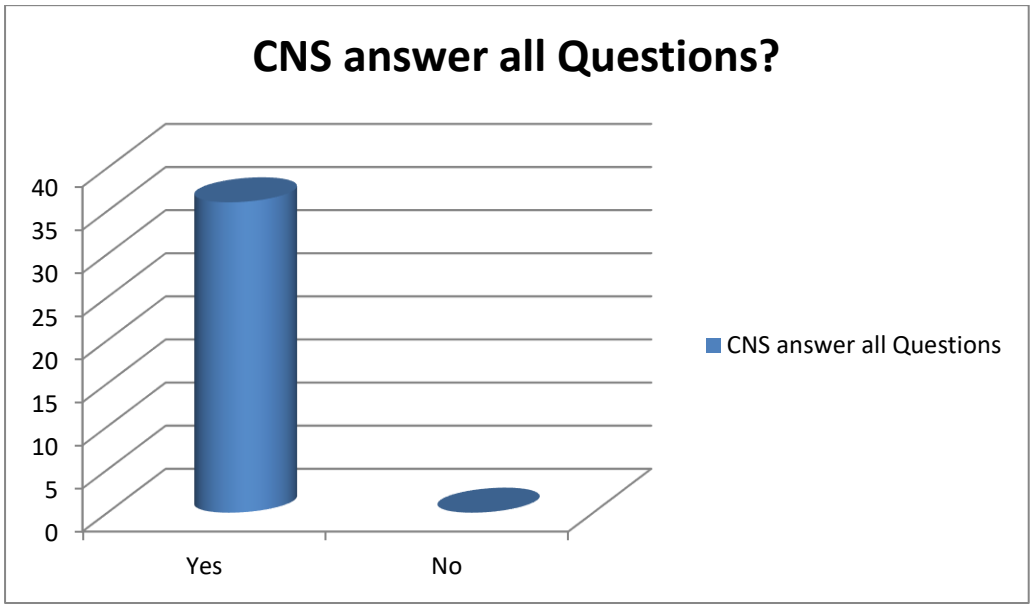
Results

Q1 How satisfied were you with the nurse specialist assessment today?

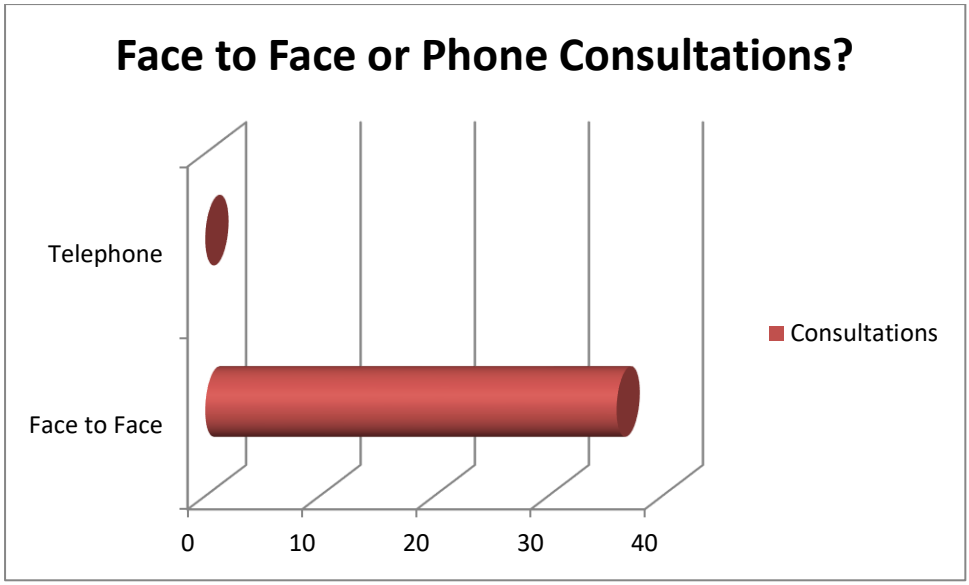
Q5 How satisfied were you with the length of the consultation today?



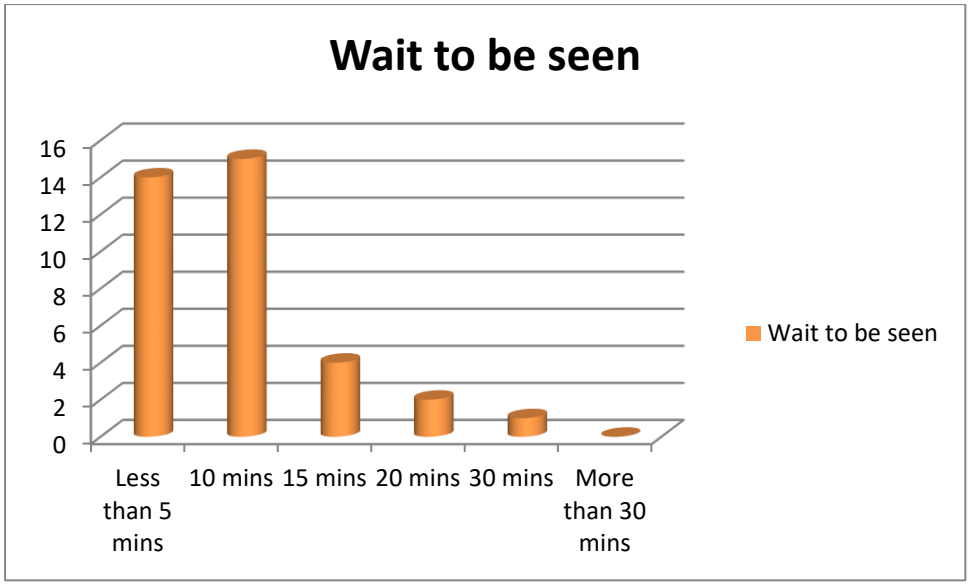
Q2 Did the CNS answer all your questions to your satisfaction?



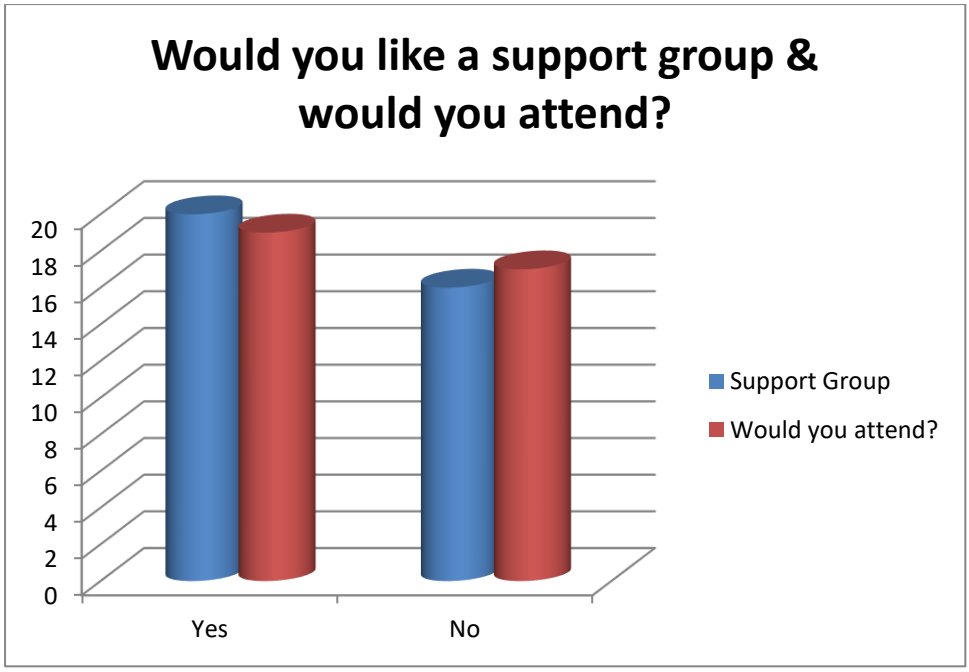
Q3 Do you prefer to see the nurse specialist face to face or would you prefer a telephone consultation?



Q4 How long did you wait to be seen by the Clinical Nurse Specialist?



Q6 & Q7



Discussion

The patient experience survey demonstrated that patients are extremely satisfied with the care from the CNS. Some regions undertake telephone follow up clinics for low risk cancer patients. Interestingly, 100% of patients who completed the survey would prefer face to face follow up when given the choice of telephone or face to face. Given that parking difficulties for patients attending outpatient clinics at the hospital are significant, to have 100% of respondents preferring face to face follow-up when given the choice is remarkable and reflects the value of face to face therapeutic relationships. Free-text comments included:

- "It's always easier to speak face to face, just in case something is not understood and a friendly face helps enormously."
- "Because they ask me questions I would not think of"
- "It's more personal"

The survey was undertaken before the COVID-19 pandemic, and since then the service has been delivered via telephone or video using the NHS 'Attend Anywhere' service. Although not formally audited, anecdotal feedback given voluntarily from patients during telephone and video consultations suggests they would like to return to face-to-face appointments in the future. The reasons for this need to be explored to understand patient preferences. A mixed approach, by either telephone, video or face to face, informed by individual patient preference, may be the way forward after the pandemic.

When patients were asked how the clinic could be improved the some of the following reponses were given:

- "I think it is a superb clinic and have always been looked after and fully supported"

- "I am very happy with my appointments and treatment"
- "Very good service"
- "It's excellent – keep going"
- "I am very satisfied and pleased to be among the people who can say "thank you" for saving my life! I can't imagine how you could improve on that! Grateful thanks."
- "It's very helpful and makes me feel my appointment is important to him"
- "Excellent staff"
- "Please ensure that this specialised treatment and help is available for all"

The above comments are representative of those given in the survey. However, there were 2 comments reminding us that waiting times can occasionally be too long: 80% of patients are seen within 10 minutes of arrival and 95% within 15 minutes. When we considered why this may be, the longer waiting times occurred when there was a newly diagnosed cancer patient in the consultant clinic which runs alongside the thyroid clinic, and the CNS interrupted the thyroid clinic to meet and support this patient.

Unfortunately, local thyroid cancer support groups do not exist: the survey was used to assess appetitite for establishment of a support group.

- 100% of patients were 'Extremely Satisfied' with the CNS assessment on the day of clinic.
- 100% of patients received answers to questions to their satisfaction
- 100% of patients prefer to see the CNS face to face rather than receive a telephone consultation
- 95% of patients were seen within 15minutes of the appointment time
- 100 of patients were satisfied with the length of the consultation
- 52% of patients would like to have a patient support group
- 52% of patients would attend a support group meeting

Limitations

The survey was administered at a single hospital, and the number of completed surveys limited, therefore the survey findings are not generalisible. Qualitative data obtained in patients' freetext responses were limited, and it is possible that interviews with patients, rather than a questionnaire tool, may have encouraged responses in greater depth. Free text comments are often seen as too subjective and unfocused to provide a babsis for action (Welch, 2010).

The survey was only available on an electronic tablet, and some patients who were not confident using the technology could decline to participate. The provision of a postal survey may have encouraged these patients to participate.

Conclusion

The nurse led thyroid cancer follow up clinic is extremely successful for patients and CNSs alike. Improving patient care and innovative ways of working were the drivers for the establishment of the

clinic in 2013, however, the clinic was established before the National Cancer Strategy (Independent Cancer Task Force, 2015) and meets the ambition for more patient centred models of follow up. Nurse led cancer follow up clinics are well established, but a concern exists about how future demand can be met when this for follow up exceeds the current supply of CNSs. The management of thyroid cancer recurrence is complex and whilst some patients may be able to self manage (as recommended in Macmillan Cancer Support's 'Recovery Package'), no current thyroid guidelines advocate this practice. Some nurses, especially CNSs, are seen as an expensive resource by some, yet in this setting, they are a more cost-effective alternative to consultant care, freeing the consultant to see new cancer patients or more complex cancer patients. The clinic is a good example of how the role of the CNS has developed to meet some of the demands of cancer care in the 21st century.

There is a trend towards telephone consultations in the NHS and has the potential benefits of convenience for the patient including the lack of need to travel to the consultation, parking at the hospital (a particular issue at the author's hospital), and no difference in the levels of patient satisfaction between face to face and telephone consultations (Hewitt et al, 2010), however, this may disadvantage patients with a hearing impairment.

Declarations of interest: none

Key points

- The incidence of thyroid cancer has been rapidly increasing in the last thirty years and most commonly affects young women. Treatment includes surgery, radio-iodine and radiotherapy
- Follow-up of thyroid cancer patients is most commonly in consultant led clinics, however national guidelines and initiatives advocate risk stratification of disease recurrence following treatment and personalised models of follow up
- Head and Neck Clinical Nurse Specialists commonly have the necessary skill set to facilitate safe follow up of this group of patients, managing risk of disease recurrence (using non-medical prescribing), long term treatment side effects such as fatigue, and provide psychological support
- Patients are extremely satisfied with the nurse led service and overwhelmingly prefer a face to face (rather than telephone) model of follow up and support despite the inconvenience and cost that this causes

CPD reflective questions:

- How can nurses continue to develop cancer services to meet the needs of patients, especially in the light of new challenges such as SARS-CoV-2 (COVID-19)?
- Do you feel confident having very complex and difficult discussions with patients in a way that they can understand?
- What skills and knowledge will help you to facilitate those conversations?
- When nurses develop highly specialised services such as the thyroid cancer follow-up clinic, how can you successfully undertake succession planning to ensure services continue to meet patient need?

References

Berglund, C. B., Gustafsson, E., Johansson, H., Bergenmar, M. (2015). Nurse-led outpatient clinics in oncology care – Patient satisfaction, information and continuity of care. *European Journal of Oncology Nursing, 19*(6), 724-730. doi: https://doi.org/10.1016/j.ejon.2015.05.007

British Thyroid Association. (2014). The British Thyroid Association Guidelines for the Management of Thyroid Cancer. Retrieved 15 February 2019 from https://www.british-thyroid-association.org/current-bta-guidelines-

Independent Cancer Taskforce. (2015). Achieving world class cancer outcomes. A strategy for England 2015-2020. Retrieved 17 February 2019, from https://www.cancerresearchuk.org/sites/default/files/achieving_world-class_cancer_outcomes_-_a_strategy_for_england_2015-2020.pdf

Cancer Research UK. (2020) TNM staging. Retrieved 11 February 2020 from: https://www.cancerresearchuk.org/about-cancer/thyroid-cancer/stages-types/tnm-staging

Cancer Research UK. (2017). Thyroid cancer incidence statistics. Retrieved 15 February, 2019, from https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/thyroid-cancer/incidence

De Leeuw, J., Prins, J., Teerenstra, S., Merkx, M. A. W., Marres, H. M., van Achterberg, T. (2012). Nurse led follow up care for head and neck cancer patients: a quasi-experimental prospective trial. *Supportive Care in Cancer. 21*(2), 537-547. doi: https://doi.org/10.1007/s00520-012-1553-1

Department of Health, Macmillan Cancer Support, & NHS Improvement. (2010) *The National Cancer Survivorship Initiative Vision.* London: Department of Health

Lewis, R. A., Neal, R. D., Hendry, M., France, B., Williams, N. H., Russell, D., . . . Wilkinson, C. (2009). Patients' and healthcare professionals' views of cancer follow-up: systematic review. *British Journal of General Practice: The Journal of the Royal College of General Practitioners, 59*(564): E248-e259. doi: https://doi.org/10.3399/bjgp09X453576

Macmilla Cancer Support (2015) The recovery package. Retireved 19 February 2019, from: https://www.macmillan.org.uk/healthcare-professionals/innovation-in-cancer-care/personalised-care

Moore, S., Corner, J., Haviland, J., Wells, M., Salmon, E., Normand, C., … Smith, I. (2002) Nurse led follow up and conventional follow up in management of patients with lung cancer: randomised trial. *British Medical Journal, 325(*7373), 1145-1147. doi: https://doi.org/10.1136/bmj.325.7373.1145

Mitchell, A.L., Gandhi, A., Scott-Coombes, D., Perros, P. (2016). Management of thyroid cancer: United Kingdom National Multidisciplinary Guidelines. *The Journal of Laryngology and Otology, 130 (Suppl. S2),* S150-S160. doi: https://doi.org/10.1017/S0022215116000578

Murchie, P., Norwood, P.F., Piertrucin-Materek, M. (2016) Determining cancer survivors preferences to inform new models of follow-up care. *British Journal of Cancer,* 115(12), 1495-1503. Doi: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5155354/

NHS Improvement (2016). *Innovation to implementation: Stratified pathways of care for people living with cancer – A 'how to' guide*. Retrieved from: https://www.england.nhs.uk/wp-content/uploads/2016/04/stratified-pathways-update.pdf

Hewitt H, Gafaranga J, McKinstry B. (2010). Comparison of face to face and telephone consultations in primary care: qualitative analysis. *British Journal of General Practice, 60*(574), e201-e212. doi: https://doi.org/10.3399/bjgp10X501831

Samuels, M., H., Kolobova, I., Semeraglio, A., Peters, D., Janowsky, J., S., Schuff, K., K., G. The effects of levothyroxine replacement or suppressive therapy on health status, mood, and cognition. *The Journal of Clinical Endocrinology and Metabolism*, 99(3): 843-851. Doi: doi: 10.1210/jc.2013-3686

Simo, R., Homer, J., Clarke, P., Mackenzie, K., Paleri, V., Pracy, P., Roland, N. (2016). Follow-up after treatment for head and neck cancer: United Kingdom Multidisciplinary Guidelines. *The Journal of Laryngology and Otology, 130 (Suppl. S2),* S208-S211. doi: https://doi.org/10.1017/S0022215116000645

To,J., Goldberg, A., S., Jones, J., Zhang, J., Lowe, J., Ezzat, S., …Sawka,A., M. (2015) A Systematic Review of Randomized Controlled Trials for Management of Persistent Post Treatment Fatigue in Thyroid Cancer Survivors. *Thyroid*, 25 (2), 198-210 DOI: https://doi.org/10.1089/thy.2014.0418

Tortora, G.J., Derrickson, B. H. (2017) *Tortora's principles of anatomy and physiology*. 15th edition. Hoboken: John Wiley & Sons

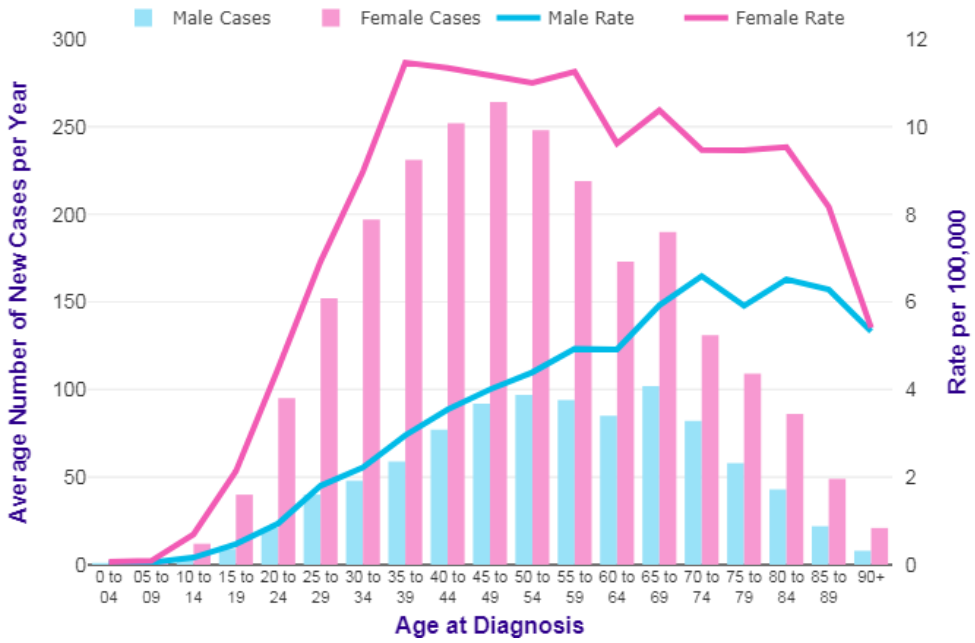
Webber, M. (2008). The role of the CNS in care of patients with head and neck cancer. *Cancer Nursing Practice, 7* (8), 35-39 Doi: 10.7748/cnp2008.10.7.8.35.c6773

Welch, S. J. (2010) Twenty years of patient satisfaction research applied to the emergency department: a qualitative review. *American Journal of Medical Quality, 25*(1), 64-72. DOI: 10.1177/1062860609352536

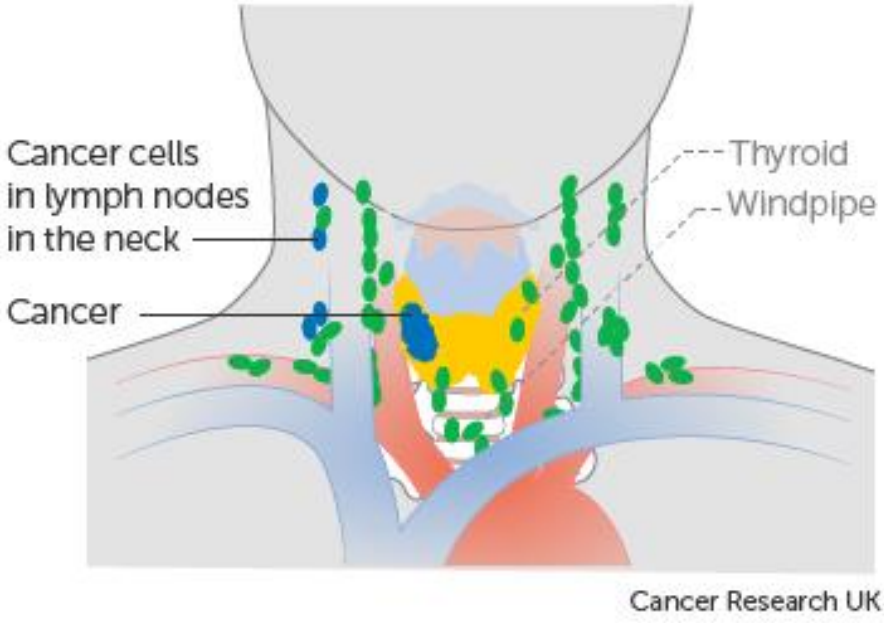
Wells, M., Semple,C.J., Lane, C., A national survey of health professionals' views on models of follow-up, holistic needs assessment and survivorship care for patients with head and neck cancer. *European Journal of Cancer Care* 2015 (24), 873-883. Doi: https://doi.org/10.1111/ecc.12285

Illustrations

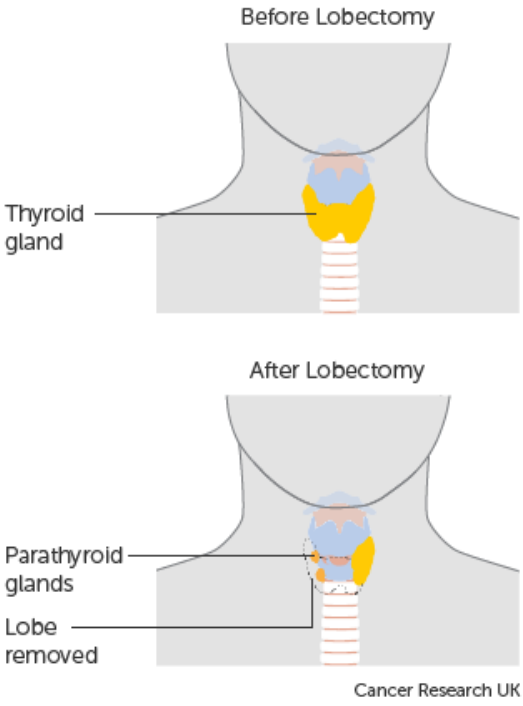
1- Average number of new cases per year – United Kingdom (Credit: Cancer Research UK. Used with permission)



2- Thyroid cancer in the right lobe and neck nodes



3- Before and after hemi-thyroidectomy / lobectomy (Credit: Cancer Research UK. Used with permission)



Case Study

James (not his real name) was referred to the nurse led thyroid clinic by a retiring oncologist. James had been in 2 yearly follow up for a number of years. James was seen in clinic to introduce the CNS and begin to establish a therapeutic relationship. James was referred for bloods and surveillance ultrasound scan of the neck and thyroid bed. Intersetingly, he had not had any ultrasound scans conducted for 7 years. A review of investigations from the previous 5 clinic appointments had shown the Thyroglbulin had been detectable but stable (Tg 3ng/mL), but there was no clear plan regarding a target Thyroid Stimulating Hormane target range. Following thyroid cancer, thyroglobulin should be undetectable – it is a dimeric protein produced by the follicular cells of the thyroid and used entirely within the thyroid gland. If thyroglobulin is detectable it raises suspicion that further disease may be present with local recurrence of the cancer or distant metastases. When James was reviewed in clinic with bloods and ultrasound scan the blood test revealed a rising thyroglobulin (Tg 5ng/mL). Following discussion with the consultant a CT chest was requested. Interestingly the consultant and the author had recently returned from a conference at which a paper was presented that theorised that there is little or no value in undertaking additional radiological investigations (other than USS) as recurrence was never detected when thyroglobulin <10ng/mL. However, we were relieved that we chose to ignore the advice as the chest CT revealed multiple chest metastases. James was discussed at the thyroid MDT and offered radio-iodine.