Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: A safer and shorter treatment for thyroid cancer

1. Summary of the impact

The HiLo trial has changed management for patients with well-differentiated thyroid cancer. Patients undergoing radioiodine ablation therapy are now given a low dose of radioactive iodine, which has fewer side effects, compared to the previous (standard) high dose. Also, to prepare patients for ablation they now have recombinant human TSH (thyrotropin alfa), which is associated with a better quality of life before and during ablation. The combination of low dose radioiodine and thyrotropin alfa means that patients can be treated as outpatients rather than inpatients. This is a more convenient treatment package, reducing health service and societal costs.

2. Underpinning research

Prior to the research described below, the standard treatment for most patients with well-differentiated thyroid cancer was as follows: they would first have a total thyroidectomy, then would go on lifelong thyroid hormone suppression therapy (THST); several weeks later they would receive high dose (3.7 GBq) radioactive iodine to destroy remaining cancer cells or residual normal thyroid tissue, at which point they would spend two to five days in hospital isolation, because of radiation protection issues; before radioiodine ablation, patients would have to temporarily stop THST, which would result in hypothyroidism, reducing quality of life.

There were two unanswered questions about this treatment, which our research aimed to address. Firstly, high dose radioiodine has side effects and increases the chance of a new cancer in the future, and there has long been discussion over whether low dose radioiodine is just as effective. Secondly, a longstanding research question was whether taking recombinant human thyroid stimulating hormone (thyrotropin alfa) before ablation (which avoids the need to stop THST) would affect treatment success rates.

In 2007, Professor Allan Hackshaw (Cancer Research UK and UCL Cancer Trials Centre) initiated and led a comprehensive systematic review of all 59 published studies into thyroid cancer, in order to address these two questions. This evaluation showed that it was not possible to reliably determine whether clinicians could use a lower radioiodine dose or not, and there was insufficient evidence to recommend thyrotropin alfa before ablation **[1]**.

As a result of these findings, Cancer Research UK (CRUK) funded a large randomised trial, led by Hackshaw and the trial Chief Investigator, Dr Ujjal Mallick (Freeman Hospital, Newcastle). The trial concept originated from Mallick and Hackshaw through the NCRN Head and Neck Cancer Clinical Studies Group. UCL was responsible for trial design, study conduct and statistical analyses, and was the trial Sponsor.

HiLo was the first ever UK national trial in thyroid cancer (438 patients recruited 2007-10), and the first factorial study in this cancer. It was independently peer-reviewed by CRUK, conducted across the UK National Cancer Research Networks and published in the New England Journal of Medicine **[2]**. These attributes confirm the high quality of this seminal and unique trial.

Treatment success rates were 85.0% in the group receiving low-dose radioiodine versus 88.9% in the group receiving the high dose; and 87.1% in the thyrotropin alfa group versus 86.7% in the group undergoing thyroid hormone withdrawal – all indicating non-inferiority. Similar results were found for low-dose radioiodine plus thyrotropin alfa (84.3%) versus high-dose radioiodine plus thyroid hormone withdrawal (87.6%) or high-dose radioiodine plus thyrotropin alfa (90.2%).

3. References to the research

[1] Hackshaw AK, Harmer C, Mallick U, Haq M, Franklyn J. 131I activity for remnant ablation in patients with differentiated thyroid cancer: a systematic review. J Clin Endocrin Metab 2007; 92(1): 28-38 http://dx.doi.org/10.1210/jc.2006-1345

[2] Mallick U, Harmer C, Yap B, Wadsley J, Clarke S, Moss L, Nicol A, Clark PM, Farnell K, McCready R, Smellie J, Franklyn JA, John R, Nutting CM, Newbold K, Lemon C, Gerrard G, Abdel-Hamid A, Hardman J, Macias E, Roques T, Whitaker S, Vijayan R, Alvarez P, Beare S, Forsyth S, Kadalayil L, Hackshaw A. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. N Engl J Med. 2012 May 3;366(18):1674-85. http://dx.doi.org/10.1056/NEJMoa1109589

Funding: Cancer Research UK (2007-2010)

Title: Randomised trial of low and high dose radioiodine, with or without, recombinant human thyroid stimulating hormone, in treating thyroid cancer.

Applicants: U Mallick (Freeman Hospital, Newcastle), A Hackshaw (UCL), C Harmer (Royal Marsden Hospital)

Value: £387,000

Sponsor: University College London

4. Details of the impact

There are >2,100 new cases of thyroid cancer each year in the UK, >48,000 in the US, and >213,000 worldwide. It is the most frequently occurring endocrine tumour, and one of the few cancers where the incidence is increasing **[a]**. Thyroid cancer, unlike most other cancers, is common among younger people (<50 years) who are still in work, and particularly women (many with children). Most cases are well-differentiated thyroid cancer (85-90% of new cases), in which the cure rate is already high; therefore new treatments that are safer, cheaper or easier to administer are the research goals.

The results of the HiLo trial provided clear evidence for a shorter and safer treatment for thyroid cancer. Cancer Research UK commented that the results of this trial "*have set a new gold standard for treating thyroid cancer, reducing radiation doses to just one third of the current level… patients taking the lower dose capsule can be treated more easily as an outpatient in hours and experience fewer side effects*" **[b]**.

The HiLo trial collected data on clinical efficacy, patient safety/harms, NHS resource use, and societal costs, allowing a comprehensive assessment of the impact in the clinical setting, as well as on healthcare costs and people's lives. Overall, the research described above showed the following benefits to patients and to the economy:

Benefits to patients:

- New treatment can be delivered as outpatient treatment which is quicker and easier for patient
- Fewer side effects (e.g. nausea and neck pain)
- Reduced chance of developing a new tumour in the next 10-30 years, which can often be more difficult to treat than the original thyroid cancer
- Improved quality of life, as THST does not need to be suspended (of particular relevance to those of working age, or caring for children – which is a relatively high proportion for this

type of cancer)

Economic benefits:

- Reduction in side effects is associated with lower costs to treat these side effects.
- Shorter hospital stay also reduces costs
- Overall 14% reduction in NHS costs using low dose radioiodine plus thyrotropin alfa compared to the previous standard of high dose plus thyroid hormone withdrawal.
- Many thyroid cancer patients are in employed work, and the average number of days taken off work during the 2-4 weeks before radioiodine treatment is 1 day (low dose) compared to 5 days (high dose).

We have disseminated the results of the HiLo trial through presentations at several international conferences in countries planning to change routine practice (including Europe, Israel and Korea) **[c]**. Our results were also widely reported in the medical press and in patient-facing resources on thyroid cancer treatment **[d]**.

In 2012, the trial findings were used to change the European licence indication for Thyrogen (thyrotropin alfa), so that it can now be used with low dose radioiodine (the previous licence was only for use with the high dose) **[e]**.

New guidelines are currently in preparation in both the UK **[f]** and US **[g]** to recommend low dose radioactive iodine and thyrotropin alfa for routine practice. In the meantime, this treatment.is already being adopted; the NCRI Clinical Studies Groups 2013 annual report, impact section, states: "*The HiLO study published in the New England Journal of Medicine is now significantly changing the clinical practice of oncologists and endocrinologists giving post-operative radio-iodine ablation to thyroid cancer patients. The dose has now been decreased considerably as a result of this study and adoption has proceeded rapidly in the UK"* **[h]**.

An informal survey of clinicians has shown that 16 centres in the UK have implemented the HiLo trial protocols since the publication. Responses included:

> "*I am routinely using HILO doses as per study in my practice ever since results were confirmed*."
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> "*Our policy…is to stratify patients needed I131 post thyroidectomy who would have fit the criteria for the Hi-Lo into 2 groups low risk or higher risk. Those patients in who remnant ablation is the aim of management (i.e. well differentiated node negative disease T1-3) are considered low risk and are treated with Thyrogen priming pre ablation and 1.1 GBq I131 as HiLo study"* **[i]**.
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> "*We have been using lower activity RAI for about 18 months"* **[j]**.
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> "*I can confirm that I have implemented one element of the HiLo study before 31/7/2013…Specifically this is the lower dose of I131*" **[k]**.

Following on from the HiLo trial, a new trial – ION – is underway to determine whether thyroid cancer patients, in whom the risk of the cancer coming back is low, need radioactive iodine (RAI) ablation at all, given that they have already had a total thyroidectomy and are being given thyroid stimulating hormone suppression (TSHS) therapy **[l]**. The control arm for this trial uses low dose radioactive iodine, demonstrating that this is now entering accepted standard practice in the 35 centres participating in the trial.

5. Sources to corroborate the impact

[a] Cancer Research UK. Thyroid cancer statistics, UK:
http://info.cancerresearchuk.org/cancerstats/types/thyroid
National Cancer Institute. Thyroid cancer, US:
http://www.cancer.gov/cancertopics/types/thyroid

[b] press release
http://www.cancerresearchuk.org/cancer-info/news/archive/pressrelease/2012-05-02-thyroid-cancer-trial-results

[c] Weblinks to international presentations of HiLo

- http://www.ies.org.il/Winter1211.asp
- http://www.gustaveroussy.fr/service.php?p_m=download&p_file=doc/agenda/conference/prog_management_thyroid_2012.pdf
- http://www.eurothyroid.com/about/clinical_trials.php
- http://www.endo.gr/?p=2650
- www.thyroid.org/wp-content/uploads/2012/04/BAT_prog_final.pdf

[d] Reporting of our trial results:

- Radioiodine for Thyroid Cancer: Less Is More. Medscape – 3 May 2012
http://www.medscape.com/viewarticle/763197
- Trial makes thyroid cancer treatment safer and shorter. HealthCanal.com – May 2012
http://www.healthcanal.com/cancers/28985-Trial-makes-thyroid-cancer-treatment-safer-and-shorter.html
- Lower-Dose Radioiodine Effective Against Thyroid Cancer. U.S. News & World Report – 2 May 2012 http://health.usnews.com/health-news/news/articles/2012/05/02/lower-dose-radioiodine-effective-against-thyroid-cancer
- For Thyroid Cancer, Thyrotropin + Low-Dose Radioiodine Effective. Doctors Lounge – May 2012 http://www.doctorslounge.com/index.php/news/pb/28786
- Thyroid cancer treatment 'now shorter and safer.' Netdoctor – 3 May 2012:
http://www.netdoctor.co.uk/interactive/news/theme_news_detail.php?id=801356066&tab_id=7
- Reference [2] is cited twice in http://www.mythyroid.com/radioactiveiodinecancer.html

[e] European Medicines Agency (EMEA) revised license for Thyrogen, Oct 2012
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000220/WC500137229.pdf

[f] Corroboration is available from the UK lead. Contact details provided.

[g] Corroboration is available from the US lead. Contact details provided.

[h] NCRI Head & Neck Cancer Clinical Studies Group 2012/13 annual report, impact section.
http://www.ncri.org.uk/csg/annual_reports/NCRI_Head_&_Neck_CSG_-_Annual_Report.pdf

[i] Correspondence from Clinical Director, Oncology, The Royal Wolverhampton NHS Trust. Available on request.

[j] Correspondence from Consultant Clinical Oncologist, Beatson Oncology Centre, Glasgow. Available on request.

[k] Correspondence from Divisional Clinical Director, The Ipswich Hospital NHS Trust. Available on request.

[l] http://clinicaltrials.gov/show/NCT01398085.