SAJS
General Surgery

Thyroglobulin – what is the postoperative threshold for the suspicion of thyroid cancer recurrence in the absence of anti-Tg antibody measurement?

M. S. PAPAGEORGIOU, M.D., PH.D.
N. LIRATZOPOULOS, PROFESSOR OF SURGERY
G. MINOPOULOS, PROFESSOR OF SURGERY
K. J. MANOLAS, PROFESSOR OF SURGERY
1st Department of Surgery, University General Hospital of Alexandroupolis, Greece

Summary

Background. Thyroglobulin (Tg) is used as a postoperative marker for the follow-up of patients with thyroid carcinoma, but there is no consensus regarding the value that may indicate possible recurrence.

Aim. To evaluate Tg levels as a marker for recurrence of thyroid carcinoma.

Subjects and methods. Demographics and survival of 80 patients who underwent total thyroidectomy for well-differentiated thyroid cancer were analysed and related to Tg levels. Tg measurements were performed when patients were euthyroid, after completion of treatment.

Results. The median Tg value was 1.3 ng/ml. Higher values were found in males, high-risk patients and patients with recurrent disease. Using the median Tg value as cut-off, patients were divided into two groups (group I ≤1.3 ng/ml and group II >1.3 ng/ml). There was a significant correlation between values >1.3 ng/ml and recurrence. When survival was related to Tg values, there was a tendency towards worse prognosis in group II. The best predictive cut-off value for recurrence was found to be 1.3 ng/ml, which had a sensitivity of 77% and a specificity of 57%.

Conclusions. Although low, a cut-off Tg level of 1.3 ng/ml represents a simple indication for further investigation in patients receiving thyroxine after completion of treatment for thyroid cancer, in the absence of measurement of anti-Tg auto-antibodies.

Well-differentiated thyroid cancer (WTC), although rare, is the most common endocrine cancer. It accounts for 1 - 5% and 0.5 - 2% of all malignancies in women and men, respectively, and is responsible for 0.25% and 0.16% of cancer-related deaths.[1-4] Total thyroidectomy has been widely accepted in the past decade to be the cornerstone of WTC treatment, often followed by ^{131}I ablation and thyroid-stimulating hormone (TSH)-suppressive hormonal substitution.

The main marker for disease recurrence during postoperative follow-up is the serum thyroglobulin (Tg) level, in the presence of normal or elevated TSH levels. The normal range of Tg values when the thyroid gland is present is 1.4 - 78 ng/ml, but there has been disagreement in the literature about both the normal range and the threshold of Tg levels in patients after total thyroidectomy for WTC.[5-7] Since Tg is the only marker for postoperative follow-up of these patients, the aim of this study was to analyse Tg levels together with epidemiological factors, and find a possible cut-off value that could raise suspicions of possible local or distant recurrence when anti-Tg auto-antibody measurement is not feasible.

Materials and methods

A retrospective study was conducted on 80 patients (20 male, 60 female; mean age 45.6 (standard deviation (SD) 15) years, range 18 - 78 years) who underwent total thyroidectomy between January 1985 and December 2004 in the First Department of Surgery at University General Hospital of Alexandroupolis, Democritus University of Thrace, Greece. All patients had final pathology reports confirming well-differentiated non-medullary thyroid cancer from the same endocrine surgeon (KJM) and his team. There were 45 papillary and 35 follicular cancers; microcarcinomas were included.

Patients' medical records and demographics, including age, sex, tumour histological type, risk group according to TNM staging, postoperative local recurrence (in the form of recurrent tumour or regional lymph node enlargement) or distal metastases (bones, lungs, etc.) and survival, were analysed and related to Tg levels in the presence of levothyroxin supplementation and suppression of TSH, using Statistical Package for the Social Sciences (SPSS), version 11.0 (SPSS Inc., Chicago, IL, USA). Statistical differences between Tg levels and any patient groups were calculated by using the Mann-Whitney-Wilcoxon rank-sum test, while the chi-square test was used for comparing two or more percentages. Using the TNM system, patients were subdivided to stages I - II (low risk) and III - IV (high risk). Postoperative recurrence was defined as a demonstrable tumour revealed by physical examination and ultrasonography, or scintigraphy and elevated Tg values.

Tg levels were measured after the whole-body scan and radioiodine ablation and once euthyroidism was achieved with normal or suppressed TSH (3 and 6 months after ^{131}I administration), using an electrochemiluminescence immunoassay (Elecsys 2010, Roche Diagnostics) with a normal range of 1.4 - 78 ng/ml and sensitivity of 0.1 ng/ml. Anti-Tg auto-antibodies were not taken into account in this study, in order to find a cut-off value of Tg that could be used by practitioners who are not able to have Tg antibodies measured, regardless of the presence or absence of anti-Tg.

Finally, an ROC curve was plotted which showed the best combination of sensitivity and specificity of postoperative Tg value for the detection of local or distal recurrence.

Results

Our series consisted of 80 patients (mean age 45.55 (SD 15.05) years, range 18 - 78 years), 20 male and 60 female (male/female ratio 1:3) with a mean follow-up time of 95.25 (SD 74.42) months. The demographic characteristics of the patients are set out in Table I. The patients were divided into age subgroups of ≤45 years or >45 years. Of the patients 56% were found to have papillary carcinoma (mixed type included) and 44% follicular carcinoma, including Hurthle cell carcinoma; 82% were low risk (stages I - II according to the TNM system) and 18% high risk (stages III - IV). Intra- or postoperative local invasion or distal metastatic disease was documented in 13 patients (16%), 11 patients presenting with local disease (10 with lymph node infiltration and 1 with recurrent tumour) and 2 with distal metastases (1 spine and 1 lungs). The overall survival rate in the study was 94%.

TABLE I. DEMOGRAPHIC CHARACTERISTICS OF THE PATIENTS

	N	%
Gender		
Male	**20**	**25.0**
Female	**60**	**75.0**
Age		
≤45 yrs	**37**	**46.3**
>45 yrs	**43**	**53.8**
Histology		
Papillary	**45**	**56.3**
Follicular	**35**	**43.8**
TNM stage		
I	**46**	**57.5**
II	**20**	**25.0**
III	**11**	**13.8**
IV	**3**	**3.8**
Risk group		
Low risk	**66**	**82.5**
High risk	**14**	**17.5**
Local/distal recurrence		
No	**67**	**83.8**
Yes	**13**	**16.3**

The median Tg value in the study was 1.3 ng/ml (0 - 4 524.8 ng/ml), while the median values in the various epidemiological categories are set out in Table II. The median TSH value in the study was 0.78 μIU/ml (range 0.01 - 1.43 μIU/ml). Higher median Tg values were found in males, in the high-risk population and in patients with local or distal recurrence (Figs 1 - 5).

Using the median value of Tg (1.3 ng/ml) as a cut-off value, patients were divided into two groups (group I, Tg ≤1.3 ng/ml, 41 patients; group II, Tg >1.3 ng/ml, 39 patients) and correlations were made with the epidemiological data. The correlation between group II and local or distal recurrence was statistically significant (p=0.026), while there was a non-significant difference between group II and the high-risk population (Table III). Further analysis

TABLE II. CORRELATION OF MEDIAN Tg VALUES WITH THE EPIDEMIOLOGICAL PARAMETERS

	Tg (ng/ml)	*p*-value
Gender		**0.038***
Male	**2.05 (0.00 - 4 524.80)**	
Female	**1.20 (0.00 - 1 529.00)**	
Age		**0.543**
≤45 yrs	**1.50 (0.00 - 4 524.80)**	
>45 yrs	**1.00 (0.00 - 1 529.00)**	
Histology		**0.866**
Papillary	**1.20 (0.00 - 4 524.80)**	
Follicular	**1.30 (0.00 - 1 529.00)**	
Risk group		**0.010**
Low risk	**1.20 (0.00 - 29.90)**	
High risk	**6.20 (0.00 - 4 524.80)**	
Local/distal recurrence		**0.005**
No	**1.20 (0.00 - 29.90)**	
Yes	**6.30 (0.30 - 4 524.80)**	

*Underlined *p*-values are significant.

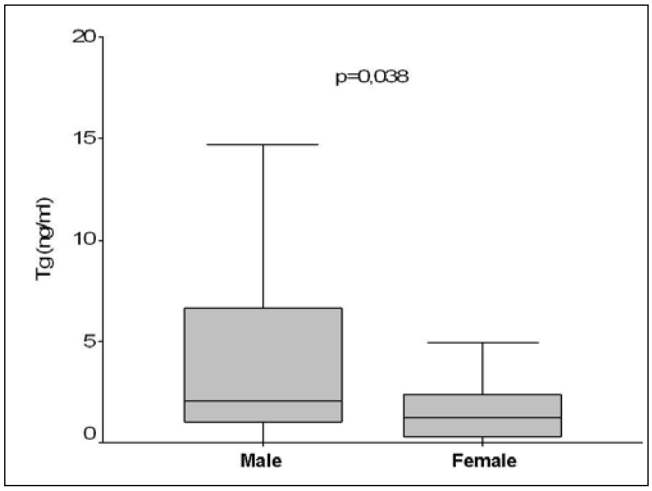

Fig. 1. Tg values in relation to gender.

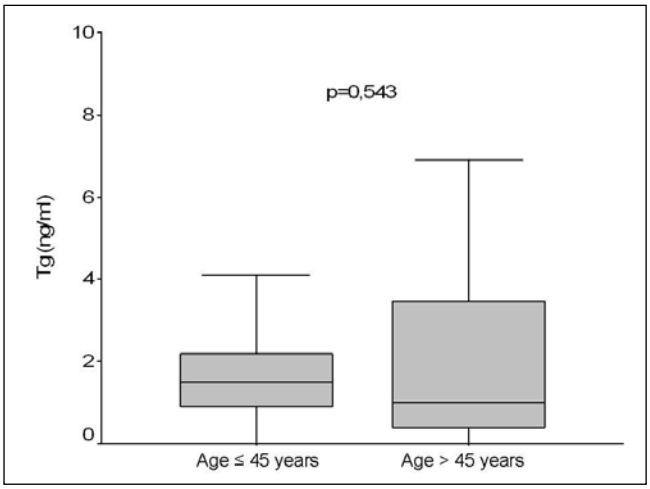

Fig. 2. Tg values in relation to age.

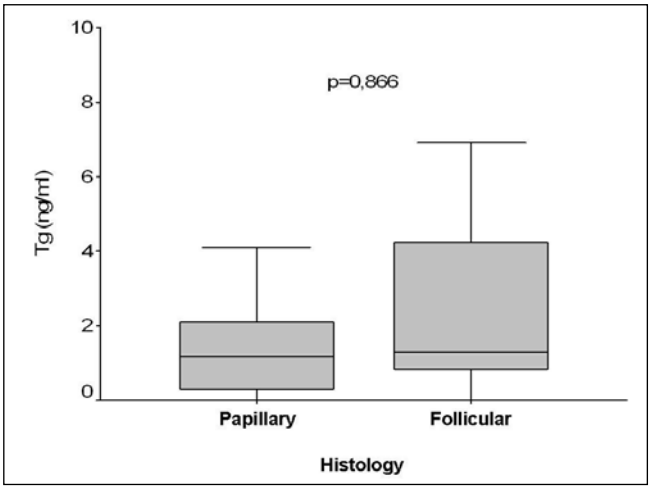

Fig. 3. Tg values in relation to histological tumour type.

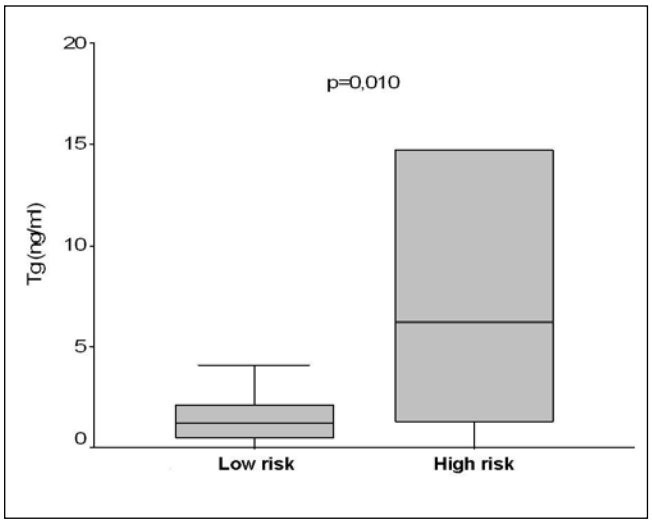

Fig. 4. Tg values in relation to risk group.

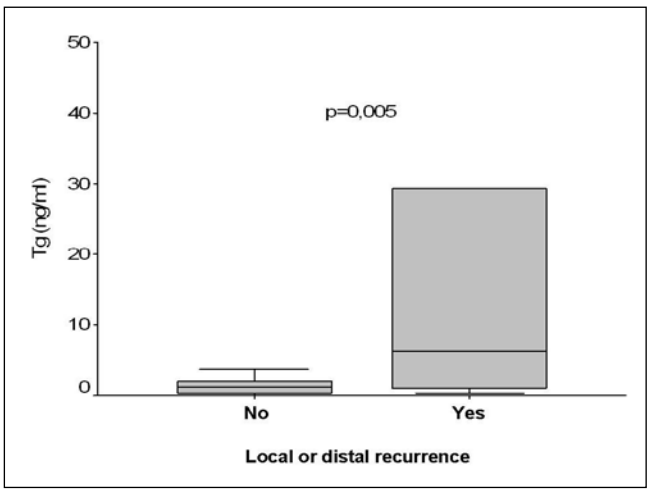

Fig. 5. Tg values in relation to presence or absence of disease recurrence.

indicated that patients in group II (Tg >1.3 ng/ml) had a 4 times higher risk of disease recurrence than patients in group I (odds ratio (OR) 4.4, 95% confidence interval (CI) 1.1 - 17.3, p=0.026).

Overall, 1-year, 5-year and 10-year survival rates were 100%, 94% and 91.8%, respectively (Fig. 6). When survival was related to Tg values, 1-year, 5-year and 10-year survival rates of patients

TABLE III. CORRELATION OF Tg GROUPS WITH THE EPIDEMIOLOGICAL PARAMETERS (%)

	Group I (Tg ≤1.3 ng/ml)	Group II (Tg >1.3 ng/ml)	*p*-value
Gender			**0.245**
Male	**40**	**60**	
Female	**55**	**45**	
Age			**0.379**
≤45 yrs	**45.9**	**54.1**	
>45 yrs	**55.8**	**44.2**	
Histology			**0.673**
Papillary	**53.3**	**46.7**	
Follicular	**48.6**	**51.4**	
Risk group			**0.062**
Low risk	**56.1**	**43.9**	
High risk	**28.6**	**71.4**	
Local/distal recurrence			**0.026***
No	**56.7**	**43.3**	
Yes	**23.1**	**76.9**	

*The underlined *p*-value is significant.

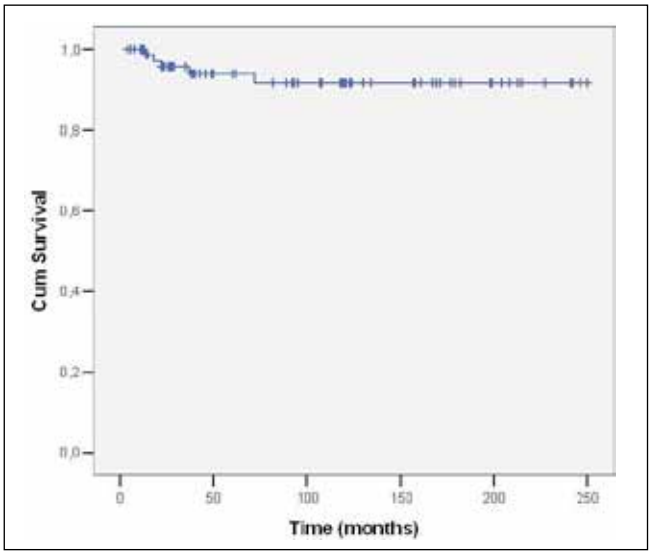

Fig. 6. Overall survival rate in the study.

in group I were 100%, 97.1% (SD 2.9%) and 97.1% (SD 2.9%), respectively, while the corresponding rates in group II were 100%, 90.9% (SD 5.1%) and 86.3% (SD 6.5%) (Table IV), differences that, although not statistically significant, show a trend towards worse prognosis in group II (Fig. 7).

ROC curve analysis was used to evaluate the value of Tg in predicting possible WTC recurrence (Fig. 8). The area under the curve (AUC) was significantly greater than 0.5 (0.811, 95% CI 0.667 - 0.954, p<0.0001), indicating that Tg is a very creditable postoperative marker for the diagnosis of recurrence. According

TABLE IV. SURVIVAL OF PATIENTS IN Tg GROUPS I AND II

	Group I (Tg ≤1.3 ng/ml)	Group II (Tg >1.3 ng/ml)
No. of patients	**41**	**39**
1 yr survival (%)	**100**	**100**
5 yrs survival (% (SD))	**97.1 (2.9)**	**90.9 (5.1)**
10 yrs survival (% (SD))	**97.1 (2.9)**	**86.3 (6.5)**
***p*-value**	**0.170**	

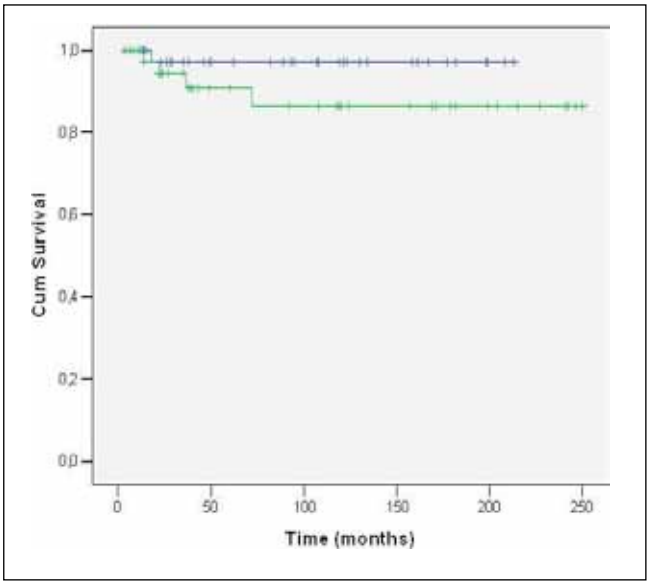

Fig. 7. Survival of Tg group I (upper line) and II (lower line).

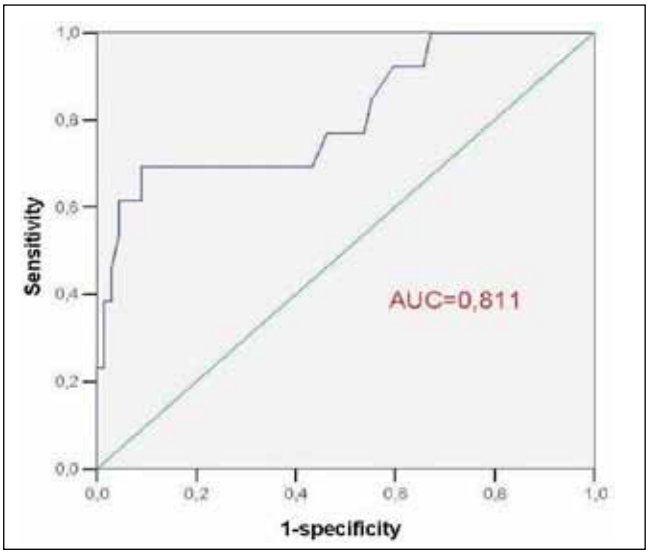

Fig. 8. ROC curve for the diagnostic accuracy of Tg for disease recurrence (p<0.0001).

to the same ROC curve, the best cut-off value between the absence and presence of disease recurrence is 1.3 ng/ml, a result that by coincidence is the same as the median value of Tg levels in this study. This cut-off value has a sensitivity of 76.9% (95% CI 39 - 90%) and a specificity of 56.7% (95% CI 44 - 69%), with a positive predictive value of 24%, a negative predictive value of 90% and overall agreement of 58.8%.

Discussion

Tg is a molecule that is produced only by thyroid cells and until the mid-20th century was thought to be found only in thyroid tissue. In 1961, Hjort first detected Tg molecules in peripheral blood, a discovery that was confirmed by Roitt and Torrigiani in 1967. Finally, van Herle proved in 1973 that the measurement of serum Tg levels is a reliable marker for the existence of WTC recurrence after total thyroidectomy.[8]

Tg is a protein that serves as an intrathyroidal storage form of thyroid hormone, which can be released into the circulation when needed; it is also detected in low levels in peripheral blood. Tg levels become undetectable 3 - 4 weeks after total thyroidectomy, other than in patients with residual disease or disease recurrence or after incomplete 'total' thyroidectomy, so in theory Tg could serve as an excellent postoperative tumour marker. In clinical practice, however, the presence of anti-Tg auto-antibodies in 10 - 20% of these patients, which falsely lowers Tg levels, limits the accuracy of the method and introduces new questions regarding the management of these patients.[8-10]

Many patients who have had thyroidectomy for WTC are followed up in centres that do not have facilities to measure anti-Tg antibodies. For this reason we attempted to find a threshold of Tg levels to arouse suspicion of disease recurrence that would be independent of the presence of anti-Tg auto-antibodies. This study has the limitation of having a lower threshold than other studies, because anti-Tg auto-antibodies falsely lower Tg levels. Our aim was to provide a safe, simple and credible value of Tg as a single stand-alone marker, above which the physician should be alerted to the possible presence of disease. In the literature, there is no consensus for the threshold value of Tg above which recurrence is suggested. Several studies suggest Tg levels ranging from 2 ng/ml up to 69.7 ng/ml.[5-7,11-13] In our study, the threshold found to have the optimal combination of sensitivity and specificity was 1.3 ng/ml, a value significantly lower than those suggested in the literature.

The sensitivity and specificity of a threshold of 1.3 ng/ml were found to be 76.9% and 56.7%, respectively. In the literature, specificity and sensitivity of Tg measurement for cancer recurrence range from 65% to 91% for sensitivity and 90% to 100% for specificity.[7,14-16] The difference between our results and others is probably because we included patients with and without anti-Tg antibodies in our study, but this was exactly our aim – to find a Tg level without taking the presence of auto-antibodies into account, so as to help practitioners, even in remote areas, to suspect recurrence and perform the necessary further tests (whole-body scan, computed tomography, FDG/PET scan, etc.), or refer to a specialist. It must be noted that the value of 1.3 ng/ml is not proposed as a solitary or definite screening test, but rather as a suspicious value that indicates further investigation by a specialist unit.

Finally, this study should not be interpreted as implying lack of concern regarding patients with Tg levels <1.3 ng/ml. Established guidelines state that they still need regular follow-up, because although the possibility of recurrence is low, it does exist (see Table III: 23.1% of patients in group I had recurrence).

In conclusion, although this series consists of a relatively small number of patients it indicates that postoperative serum Tg levels after total thyroidectomy can be used relatively safely as a diagnostic marker in patients with papillary and follicular thyroid cancer when anti-Tg auto-antibody measurement is not possible. The cut-off value proposed to prompt suspicion of recurrence is 1.3 ng/ml. Although low, this value is a simple means of indicating that further investigation of these patients in specialised departments is needed, if measurement of anti-Tg auto-antibodies is not possible. We agree that Tg auto-antibody measurement has an impact on the Tg values, but this study was designed to test the hypothesis that when the former is not available, Tg alone can serve as a reasonably credible tumour marker. Measurement of the anti-Tg auto-antibody level is still recommended as the optimal strategy when using Tg as a follow-up tumour marker.

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News

Adding smiles to children's lives

Twenty children underwent reconstructive surgery during the 'Adding Smiles to Life with Adcock Ingram' Smile Week held from 25 to 29 July at Red Cross Hospital War Memorial Children's Hospital, Cape Town. Thanks to the Smile Foundation and Adcock Ingram Healthcare, these children's parents, families and communities can 'celebrate the fact that they have a beautiful smile and can go off to school when they're older without fear of being teased or isolated', said Moira Gerszt, Chief Operating Officer of the Smile Foundation.

The Smile Foundation's partnership with Adcock Ingram began last year. 'Adcock Ingram is humbled by being part of this philanthropic initiative,' said Dr Jonathan Louw, CEO for Adcock Ingram Healthcare.

'The funding that Adcock Ingram contributes towards these life-changing operations not only lessens the deformity of these children, but ensures that the every child is able to swallow both solids and liquids with ease. Our partnership with Smile Foundation reiterates our commitment to adding value to life, and changing one child at a time,' said Louw.

The Smile Foundation has partnered with academic hospitals in South Africa to help underprivileged children with facial conditions, alleviating backlogs in the hospitals, encouraging skills transfer, offering psychological help before and after surgery, and supporting hospital infrastructure.

The Smile Foundation's partnership with Red Cross Children's Hospital is now in its second year. As part of the partnership the Smile Foundation funds the additional resources necessary and pays for the surgery. The hospital provides the infrastructure, staff, care, treatment and expertise.

The success of the Smile Week model has been widespread. To date almost 700 children around the country have benefited from surgery through the partnership with state academic hospitals. In the Western Cape, 80 children have been helped during the various Smile Weeks held in the province.

For more information, contact Sanri van Wyk, Taryn Fritz Public Relations.