Author/s:
Tan, JHJ;Malloy, MJ;Brotherton, JML;Saville, M

Title:
Compliance with follow-up Test of Cure and outcomes after treatment for high-grade cervical intraepithelial neoplasia in Victoria, Australia

Date:
2020-06-01

Citation:
Tan, J. H. J., Malloy, M. J., Brotherton, J. M. L. & Saville, M. (2020). Compliance with follow-up Test of Cure and outcomes after treatment for high-grade cervical intraepithelial neoplasia in Victoria, Australia. Australian and New Zealand Journal of Obstetrics and Gynaecology, 60 (3), pp.433-437. https://doi.org/10.1111/ajo.13115.

Compliance with follow-up Test of Cure and outcomes after treatment for high-grade cervical intra-epithelial neoplasia in Victoria

Jeffrey H.J. TAN[1,2*], Michael J. MALLOY[3,4], Julia ML BROTHERTON[3,4], Marion SAVILLE[2,5].

[1] Department of Oncology & Dysplasia, The Royal Women's Hospital, Parkville, Australia

[2] Department of Obstetrics and Gynaecology, University of Melbourne, Melbourne, Australia

[3] VCS Population Health, VCS Foundation, East Melbourne, Australia

[4] Melbourne School of Population and Global Health, University of Melbourne, Victoria, Australia

[5] VCS Foundation, Carlton, Australia.

* Address for correspondence:

Dr. Jeffrey Tan, Suite 10, Level 2, Royal Women's Hospital, Flemington Road, Parkville, Victoria, 3052, Australia.

T: +61 3 9816 8775; Email: jeff.tan@thewomens.org.au

Disclosure of interests

JT, MM have no Competing interests:

JB, MS VCS Pathology (a branch of VCS Foundation) has received free/donated HPV test kits from Roche, Seegene, Cepheid, and Becton Dickinson as part of unrestricted laboratory testing, comparative studies and investigator initiated research as part of our role as an HPV screening reference laboratory.

Funding

The authors did not receive any funding for this study.

Author names, positions and institutional affiliations

1) Dr. Jeffrey H.J. Tan
   Consultant Gynaecolgist
   Royal Women's Hospital, Parkville, VIC 3052.

2) Dr, Michael Malloy
Biostatistician, VICNISS Coordinating Centre
The Peter Doherty Institute for Infection and Immunity
792 Elizabeth Street | Melbourne | Victoria
Email: Michael.Malloy@mh.org.au

3) Assoc Prof Julia Brotherton
Medical Director, VCS Population Health
Level 6, 176 Wellington Parade, East Melbourne, VIC, 3002.
Email: jbrother@vcs.org.au

4) Assoc Prof Marion Saville
Executive Director, VCS Foundation
265 Faraday St, Carlton, VIC, 3053.
Email: msaville@vcs.org.au

Blinded sentences

Abstract
De-identified data were retrieved from the Victorian Cervical Cytology Registry (VCCR) in Melbourne as at April 24, 2015.

Materials and Methods
Cervical screening tests, treatments for screen detected abnormalities and related histopathology results are recorded in the Victorian Cervical Cytology Registry (VCCR) for all women resident in Victoria, Australia.
De-identified data were retrieved from the VCCR for women with HSIL who had excisional treatment (whether HSIL diagnosed at pre-treatment punch biopsy or HSIL at excision) between 1st Jan 2007 and 31st Dec 2011.

Results

Between 2007 and 2011, 8,478 women with HSIL had excisional treatment recorded in VCCR.

The median number of follow-up episodes post treatment was six, episodes being any cytology, HPV or histopathology test, either alone or in any combinations as recorded on the VCCR.

References

6. Victorian Cervical Cytology Registry Statistical Report 2015: p14. https://www.vccr.org/site/VCCR/filesystem/documents/dataandresearch/StatisticalReports/17030_VCS_StatsReport15_ART.3.pdf (accessed Sept 2019)

Table 1: Type of High Grade Squamous Intraepithelial Lesion (HSIL), treatment method and Test of Cure (ToC) completion in the Victorian Cervical Cytology Registry

Table 2**:** Follow up after treatment in 2007-2011 for High Grade Squamous Intraepithelial Lesions (HSIL) as recorded in the Victorian Cervical Cytology Registry

DR. JEFFREY H. J. TAN (Orcid ID : 0000-0002-0226-8647)

Article type : Original Manuscript

Compliance with follow-up Test of Cure and outcomes after treatment for high-grade cervical intra-epithelial neoplasia in Victoria

Short title: Test of Cure after treatment for HSIL of Cervix

Word count Abstract: 247

Main Text: 1962

Table count: 2

Figure count: 0

Keywords**:** HPV testing, CIN, HSIL, Test of Cure

ABSTRACT

Background

Test of Cure (ToC), a combination of testing for oncogenic human papillomavirus (HPV) and cytology, at twelve months post treatment and annually thereafter, was approved in Australia for follow-up of women treated for high grade squamous intraepithelial lesions (HSIL) of the cervix in 2005.

Aims

To determine amongst women resident in Victoria, Australia, the compliance with ToC and the incidence of recurrence up to five years after successful ToC.

Materials and Methods

A retrospective analysis of women with HSIL (diagnosed at pre-treatment punch biopsy or at excision) who had excisional treatment between 1st Jan 2007 and 31st Dec 2011. De-identified data were retrieved from the Victorian Cervical Cytology Registry (VCCR) in Melbourne as at April 24, 2015. Successful TOC is defined as the occurrence of two consecutive normal (negative) co-tests. Recurrence after treatment is defined by histologically detected HSIL or greater.

Results

8,478 women had excisional treatment for HSIL with 448 (5.5%) experiencing recurrence. Only 2,253 (26.6%) women successfully completed ToC, with a decreasing likelihood of ToC completion by time since year of treatment (32.0% in 2007 compared with 20.9% in 2011). Only one (0.08%) woman had HSIL on histology after successful ToC. From the 2007 cohort, 555 (32.0%) women completed ToC successfully and no HSIL recurrence occurred thereafter (median subsequent follow-up period of 4.7 years).

Conclusions

Our study confirmed that women who successfully complete ToC can be returned to 5-year routine screening. However, more concerted efforts are needed to ensure that all women treated complete ToC.

Introduction

In 2005, Test of Cure (ToC) was approved in Australia by the National Health and Medical Research Council (NHMRC) for follow-up of women treated for high grade squamous intraepithelial lesions (HSIL (cervical intraepithelial neoplasia (CIN)2/3)) of the cervix.[1] This combination of testing for oncogenic human papillomavirus (HPV) and cytology is recommended at twelve months post treatment and annually thereafter, until two consecutive normal (negative) co-tests occur, meaning that ToC has been completed and the woman can return to routine cervical screening, given that her risk of HSIL or cancer is now similar to

the population risk and no longer elevated.[2,3] Despite this recommendation, a report from Western Australia in 2015 showed that a significant number of Australian women did not enter (~37%) or complete (~50%) the ToC management pathway.[4] Following the introduction of the new primary HPV cervical screening program in Australia in December 2017, women will now be returned to routine 5-yearly screening after completing ToC successfully.[5]

Our aims were to conduct a retrospective analysis to determine amongst women resident in Victoria, Australia:

i. The compliance with ToC for women treated for HSIL.
ii. Outcome after successful ToC, with recurrence defined by histologically detected HSIL.
iii. Whether HPV testing alone is comparable to ToC post-treatment in providing a high negative predictive value for risk of recurrence.
iv. The safety of returning women to routine 5-year screening after completing ToC.

Materials and Methods

Cervical screening tests, treatments for screen detected abnormalities and related histopathology results are recorded in the Victorian Cervical Cytology Registry (VCCR) for all women resident in Victoria, Australia. This role was transferred to the National Cancer Screening Register in 2019. The registry data included almost all women as only 0.03% of women opt off the registry.[6] De-identified data were retrieved from the VCCR for women with HSIL who had excisional treatment (whether HSIL diagnosed at pre-treatment punch biopsy or HSIL at excision) between 1st Jan 2007 and 31st Dec 2011. HSIL was coded as CIN2, CIN3 and high grade CIN_NOS (not otherwise specified) in the register. The date of censoring for follow-up post treatment was April 24, 2015, allowing the 'year 2007' cohort to have adequate time for five years of follow-up after successfully completing ToC. The median duration of follow-up for the '2007 cohort' was 7.6 years (range: 0.02 – 8.2 years) and for those who successfully completed ToC, their median duration of follow-up after was 4.7 years (range: 0.15 – 6.3 years). Follow-up duration was in the range of 3 years 3 months to 8 years 3 months for all women in this study,

A descriptive analysis of the data was undertaken to determine frequency of ToC, histopathology and cervical cytology alone at follow-up. In the calculations, the denominator for each outcome only includes women with a follow-up result documented for that outcome. Trends in proportions were assessed using the Wilcoxon-type non-parametric test for trend

across ordered groups. All statistical analysis was performed in Stata/IC 12.1 for Windows (StataCorp LP, College Station, TX, USA).

This study was approved by the Human Research Ethics Committee, Department of Health in the State of Victoria (Ref: 05/11).

Results

Between 2007 and 2011, 8,478 women with HSIL had excisional treatment recorded in VCCR. The distribution of HSIL lesions were sub-classified as CIN3 (5,127 (60.5%)), CIN2 (3,176 (37.4%)) and CIN_NOS (175 (2.1%)). Lesions were predominantly treated by loop excision (LEEP/LLETZ) (n=7,494 (88.4%)) with the remainder treated by cold knife cone biopsy (CKC) (n=984 (11.6%)). The median number of follow-up episodes post treatment was six, episodes being any cytology, HPV or histopathology test, either alone or in any combinations as recorded on the VCCR. There were 2,253 (26.6%) women who successfully completed ToC. Of the 6,225 (73.4%) women who did not complete ToC, 2,400 (38.6%) did not have any HPV tests and 2,154 (34.6%) had only one HPV test. The overall non-compliance rate, when less than 2 HPV tests were performed, was 55.7% (4,554) for the whole 2007-2011 cohort. The remaining 1,671 (26.8%) who had more than 2 HPV tests were deemed to have an incomplete ToC because of (i) positive HPV test irrespective of cytology, (ii) abnormal cytology associated with negative HPV test, (iii) HPV tests too close together (i.e. less than 9 months apart) and (iv) HPV test and corresponding cytology test too far apart in time (i.e. greater than 3 months between them). There was a decreasing likelihood of ToC completion by year of initial HSIL treatment, 32.0% in 2007 compared with 20.9% in 2011 (test of trend p-value < 0.001) (Table 1).

During follow-up post treatment, 1,823 (22.3%) women had further histopathology reported, comprising a target punch biopsy in 1,185 (14.5%), loop excision of cervix (LEEP/LLETZ) in 225 (2.8%), cold knife cone biopsy (CKC) in 72 (0.9%), hysterectomy in 225 (2.8%) and other specimens in 116 (1.4%). Others included endocervical curettage, dilatation and curettage (endometrial biopsy), polypectomy, vaginal vault or vulval biopsy, and amputation of cervix. Four hundred and forty-eight women (5.5%) had histologically detected HSIL or greater post treatment, with three Adenocarcinoma in situ (AIS) and 19 cancers diagnosed. For these 19 women with cancers, the median time to detection was 0.53 years with a range of 0.08 - 3.5 years.

Of the 6,355 women who had no histology during follow-up, results of their cytology (either stand alone or as part of ToC) were as follows: low grade (LSIL) 1,264 (19.9%), possible

high grade (pHSIL) 168 (2.6%), high grade (HSIL) 58 (0.9%) and glandular abnormality 8 (0.1%). Three hundred (3.5%) women had no cytology or histology follow-up post treatment (Table 2).

Overall 2,253 women successfully completed ToC, of whom 1,396 (62.0%) were treated for CIN3 and 1,976 (87.7%) with Loop excision. Most women who completed (1,573 (69.8%)) had two consecutive negative co-tests after treatment, with a cumulative 91.1% (2,052) completing ToC after three tests and 96.9% (2,189) after four tests. Only one (0.08%) woman had HSIL on histology after successful ToC, with eight (0.63%) having LSIL. The follow-up cytology after successful ToC in the 1,216 (54.0%) women who had no further histology yielded 46 (3.8%) LSIL and 5 (0.41%) pHSIL. The median years of follow-up post successful ToC was 2.27 years (range: 0.02 – 6.42years). Five-hundred and ninety-one women (26.2%) had one follow-up screen, 395 (17.5%) had two follow-up episodes, 283 (12.6%) had more than two episodes, whereas 989 women (43.9%) did not have any follow-up after successful ToC.

We examined whether two negative HPV tests are comparable to ToC post-treatment in having a high negative predictive value for risk of recurrence. In the 2007-2011 cohort, 2,395 women had their first two HPV tests post initial treatment return negative results. Of these women, 579 (24.2%) had one follow-up screen, 432 (18.0%) had two follow-up episodes, 529 (22.1%) had more than two episodes and 872 (36.4%) did not have any follow-up after the two negative HPV tests. Histopathology taken during follow-up after the two negative HPV tests detected four HSIL (0.26%) and 30 LSIL (2.0%). Among 1,410 women with no histology but who had cytology during follow-up, LSIL was reported in 72 (5.1%), pHSIL in 4 (0.28%) and HSIL in one woman (0.07%). The rate of histologically confirmed HSIL detection (i.e. recurrence) following two negative HPV tests was extremely low and comparable to the rate in the cohort that completed ‘Test of Cure’ (0.26% HPV vs 0.08% ToC; $p = 0.202$).

With the introduction of a new primary HPV cervical screening program in Australia in December 2017, women will be returned to routine 5-year screening after successfully completing ToC. We examined the 2007 cohort, who had a median follow-up of 7.6 years after treatment, to determine the outcomes of 5 years follow-up after successful ToC. Of the total 2007 cohort of 1,737 women, 555 (32.0%) women completed ToC successfully, with a median subsequent follow-up period of 4.7 years. Of these women, 137 (24.7%) had one follow-up screen, 134 (24.1%) had two follow-up episodes, 138 (24.9%) had more than two

episodes and 146 (26.3%) did not have any follow-up after completing ToC. There were no HSIL and only two LSIL (0.49%) on histology at follow-up after completing ToC.

Discussion

The non-compliance rate with the ToC protocol for women treated for HSIL was 55.7% in our study, similar to a report from Western Australia.[4] Only 26.6% of women treated had completed ToC successfully. This is quite a disappointing figure, with most of the failures due to non-compliance and decreasing compliance for more recently treated women, notwithstanding the shorter follow-up time since these women's treatment. This is despite routine reminders to attend for follow-up being sent to women from the register at 9 months post treatment and at 9 months/15 months after each subsequent HPV/LBC co-test until completed TOC. However, no routine reminders were provided to clinicians. A particular difficulty, until May 2017 when liquid based cytology became eligible for reimbursement as part of the national screening program, was that conventional cytology samples were unsuitable for HPV testing. Electronic reminder systems in use in primary care were unable to capture in sufficient detail the laboratory recommendation for a TOC at 12 months and would instead record the need for a 12 month repeat. Thus if a conventional test was collected from the recalled woman, the laboratory was unable to process the sample as a TOC even if they were aware from the woman's screening history that this was indicated. Even if the practitioner was then advised that a TOC was recommended, it would require further recall of the woman and a repeat specimen collection. These process issues are likely to explain, at least partially, the suboptimal compliance with the TOC protocol.

Four hundred and forty-eight women (5.5%) had histologically detected HSIL or greater post treatment but only one (0.08%) woman had HSIL after successful ToC. Our 2007 cohort of 1,737 women, who had a median follow-up of 7.6 years after treatment, had no HSIL recurrence after successful ToC. The low incidence of HSIL recurrence, and its early detection when it did occur, could be due to clinical follow-up being performed at 6-months post treatment in some women, resulting in HSIL recurrence, which may in fact be due to incomplete initial treatment (i.e. persistence not recurrence) being detected prior to first ToC at 12-months post treatment. Other reports also confirm that women with two negative results on co-testing have a low risk of HSIL recurrence, with a 5-year risk of CIN2 or higher of between 1.0%[7] and 1.5%[8]. This should give practitioners and women confidence in the safety of Australian guidelines which recommend returning women to routine 5-yearly screening after successful ToC.

In women whose first two HPV tests post initial treatment returned a negative result, irrespective of cytological findings, four (0.26%) had HSIL recurrence on histology at follow-up thereafter. This compares with one (0.08%) woman with HSIL after successful ToC, a non-statistically significant difference in HSIL recurrence at follow-up (p-value = 0.202). However, our study was not randomised and, until such a randomised study is done to compare HPV testing alone against co-testing for post treatment follow-up or further robust population level data become available and guidelines updated accordingly, clinicians should continue to utilise co-testing as ToC as per current guidelines.

Our study confirms that women who successfully complete ToC after treatment for HSIL of the cervix can be returned to 5-year routine screening. However, more concerted efforts are needed to ensure that all women treated complete their ToC. Communication between specialists who undertake treatment and medical practitioners, often family practitioners who routinely follow-up women post treatment and for further screening, is critical to ensure women complete ToC. Also vital is easy access to a woman's screening history by all practitioners involved in her care, as well as targeted and timely reminders and communications for indicated follow-up tests from the National Cervical Screening Program.

References

1. Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities. National Health and Medical Research Council ISBN: 0 642 82714 1

2.Uijterwaal MH, Kocken M, Berkhof J, et al. Posttreatment assessment of women at risk of developing high-grade cervical disease: proposal for new guidelines based on data from the Netherlands. J Low Genit Tract Dis 2014 Oct;18(4):338-343.

3. Australian Institute of Health and Welfare. Report on monitoring activities of the National Cervical Screening Program Safety Monitoring Committee. Cancer series 80. Cat. no. CAN 77. Canberra: AIHW; 2013: p20-21. Available from: http://www.aihw.gov.au/publication-detail/?id=60129545158 (accessed Sept 2019)

4. Munro A, Spilsbury K, Leung Y, et al. The human papillomavirus Test of Cure: A lesson on compliance with the NHMRC guidelines on screening to prevent cervical cancer. Australian and New Zealand Journal of Obstetrics and Gynaecology 2015; 55: 185–190

5. National Cervical Screening Program: Guidelines for the management of screen-detected abnormalities, screening in specific populations and investigation of abnormal vaginal

bleeding. March 2017 ISBN: 978-1-925136-17-3: p161-163
http://wiki.cancer.org.au/australiawiki/images/a/ad/National_Cervical_Screening_Program_guidelines_long-form_PDF.pdf (accessed Sept 2019)
6. Victorian Cervical Cytology Registry Statistical Report 2015: p14.
https://www.vccr.org/site/VCCR/filesystem/documents/dataandresearch/StatisticalReports/17030_VCS_StatsReport15_ART.3.pdf (accessed Sept 2019)
7. Kocken M, Helmerhorst TJ, Berkhof J, et al. Risk of recurrent high-grade cervical intraepithelial neoplasia after successful treatment: a long-term multi-cohort study. Lancet Oncol 2011 May;12(5):441-450
8. Katki HA, Schiffman M, Castle PE, et al. Five-year risks of CIN 3+ and cervical cancer among women with HPV-positive and HPV negative high-grade Pap results. J Low Genit Tract Dis 2013 Apr;17(5 Suppl 1):S50-55

Table 1: Type of High Grade Squamous Intraepithelial Lesion (HSIL), treatment method and Test of Cure (ToC) completion in the Victorian Cervical Cytology Registry

Year of cohort	HSIL treated	Type of HSIL			Method of treatment		ToC Completed	ToC incomplete*
	Total	CIN3	CIN2	CIN_NOS	Loop Excision	Cold knife Cone biopsy		
2007	1,737	1,024 (59.0%)	681 (39.2%)	32 (1.8%)	1,533 (88.3%)	204 (11.7%)	555 (32.0%)	1,182 (68.0%)
2008	1,805	1,088 (60.3%)	679 (37.6%)	38 (2.1%)	1,585 (87.8%)	220 (12.2%)	508 (28.1%)	1,297 (71.9%)
2009	1,682	1,017 (60.5%)	625 (37.1%)	40 (2.4%)	1,485 (88.3%)	197 (11.7%)	469 (27.9%)	1,213 (72.1%)
2010	1,586	966 (60.9%)	590 (37.2%)	30 (1.9%)	1,423 (89.7%)	163 (10.3%)	372 (23.5%)	1,214 (76.5%)
2011	1,668	1,032 (61.9%)	601 (36.0%)	35 (2.1%)	1,468 (88.0%)	200 (12.0%)	349 (20.9%)	1,319 (79.1%)
2007-2011	8,478	5,127 (60.5%)	3,176 (37.4%)	175 (2.1%)	7,494 (88.4%)	984 (11.6%)	2,253 (26.6%)	6,225 (73.4%)

*Incomplete ToC: either not having 2 ToC or not had 2 consecutive negative co-test within time frame

CIN_NOS (HSIL - not otherwise specified)

Table 2**:** Follow up after treatment in 2007-2011 for High Grade Squamous Intraepithelial Lesions (HSIL) as recorded in the Victorian Cervical Cytology Registry

		Year of cohort 2007-2011			Year of cohort 2007 (n=1,737)
		After initial treatment 2007 – 2011 n=8,478	After ToC[c] n=2,253 (26.6%)	After 2 negative HR-HPV tests[1] n=2,395 (28.2%)	After ToC[c] n=555 (32.0%)
No follow up		300 (3.5%)	989 (43.9%)	872 (36.4%)	146 (26.3%)
Histology during follow-up[2]		n=8,178	n=1,264	n=1,523	n=409
	Negative	885 (10.8%)	35 (2.8%)	73 (4.8%)	21 (5.1%)
	LSIL	429 (5.2%)	8 (0.63%)	30 (2.0%)	2 (0.49%)
	HSIL	426 (5.2%)	1 (0.08%)	4 (0.26%)	0
	Glandular abnormality	3 (0.04%)	0	0	0
	Cancer	19 (0.23%)	0	0	0
	Others	61 (0.75%)	4 (0.32%)	6 (0.39%)	0
Procedures during follow-up[2]	Punch biopsy	1,185 (14.5%)	23 (1.8%)	75 (4.9%)	9 (2.2%)
	Loop excision	225 (2.8%)	3 (0.24%)	7 (0.45%)	2 (0.49%)
	Cold knife cone biopsy	72 (0.88%)	0	0	0
	Hysterectomy	225 (2.8%)	12 (0.95%)	16 (1.0%)	9 (2.2%)
Cytology, where no histology performed at follow up		n=6,355	n=1.216	n=1,410	n=386
	Negative	4,852 (76.3%)	1,163 (95.6%)	1,330 (94.3%)	370 (95.9%)
	LSIL	1,264 (19.9%)	46 (3.8%)	72 (5.1%)	16 (4.1%)
	pHSIL	168	5	4	0

		(2.6%)	(0.41%)	(0.28%)	
	HSIL	58 (0.91%)	0	1 (0.07%)	0
	Glandular abnormality	8 (0.13%)	0	0	0
	Unsatisfactory	5 (0.08%)	2 (0.16%)	3 (0.21%)	0

ToC[c] (Test of Cure): successfully completed ToC

LSIL Low Grade Squamous Intraepithelial Lesion

pHSIL Possible High Grade Squamous Intraepithelial Lesion

Others include unsatisfactory and non-cervical specimens

[1] After first 2 negative HPV tests post treatment (ignoring cytology)

[2] Denominator for calculations excluded those with no follow up