World Health Organization

WHO guidelines for the use of thermal ablation for cervical pre-cancer lesions

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ABBREVIATION AND ACRONYMS

C4GEP	WHO Comprehensive cervical cancer control: a guide to essential practice
CIN	Cervical intraepithelial neoplasia
CKC	Cold knife conization
GDG	Guideline Development Group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
LEEP	Loop electro excision procedure
LLETZ	Large loop excision of the transformation zone
LMIC	Low- and middle-income countries
LSIL	Low-grade squamous intraepithelial lesion
PICO	Population, intervention, comparison and outcome framework
SCJ	Squamocolumnar junction
TZ	Transformation zone
VIA	Visual inspection with acetic acid
WHO	World Health Organization

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Executive summary

INTRODUCTION

It is estimated that more than 311 000 women die of cervical cancer each year. Of these deaths, 91% occur in low- and middle-income countries. Demographic changes and a lack of action mean that the number of deaths per year is projected to reach 460 000 by 2040.

Screening programmes have dramatically reduced cervical cancer rates in high-income countries. Screening using a cytology-based method and histological confirmation of cervical intraepithelial neoplasia (CIN) is typically followed by treatment such as cryotherapy, large loop excision of the transformation zone (LLETZ), and cold knife conization (CKC). However, in low- and middle-income countries, it has not been possible to obtain high population coverage with cytology-based screening, and other tests are being used to screen, including visual inspection with acetic acid (VIA) and more recently, DNA/RNA tests for human papillomavirus (HPV). Screen-and-treat algorithms, where women who are positive for a screening test are treated with ablative treatment (destruction of the cervical transformation zone including the lesion), have been implemented.

Cryotherapy is a World Health Organization (WHO) recommended ablative treatment, but one major disadvantage is the need for a refrigerant gas (N_2O or CO_2). The gas containers are bulky and heavy to transport and some areas of low- and middle-income countries (LMICs) may have supply issues. In addition, frequent refilling of freezing gas can be costly. Thermal ablation, also called "cold coagulation" or thermocoagulation, is another ablative treatment for CIN. The equipment is simple, lightweight (devices can weigh much less than 2 kg), and is easily portable to LMIC field clinics. Treatment is based on a 20–40 second application (multiple if needed) of a reusable metallic probe that is electrically heated to approximately 100 °C, leading to epithelial and stromal destruction. Like cryotherapy, thermal ablation is provided by a variety of health care personnel, including primary health care workers, and typically performed without anesthesia.

RATIONAL FOR THE GUIDELINES

Thermal ablation is not included in the latest version of the WHO guidelines for treatment of cervical intraepithelial neoplasia 2–3 and adenocarcinoma in situ, nor in the *WHO Comprehensive cervical cancer control: a guide to essential practice* (C4GEP) manual, but evidence is accumulating to support its inclusion, and there were requests from countries and WHO partners to issue recommendations on the use of thermal ablation for the treatment of cervical precancer lesions.

OBJECTIVES

The objectives of these guidelines are

- to provide evidence-based guidance on the use of thermal ablation to treat cervical precancer; and
- to support countries to update their national guidelines for the use of thermal ablation for cervical precancer.

METHODS

These guidelines were developed using the *WHO Handbook for guideline development*. A Guideline Development Group (GDG) was established that included experts, clinicians and researchers in cervical cancer prevention and treatment, health programme directors, and methodologists. Conflicts of interests were managed according to WHO rules. An independent systematic review team and methodologist synthesized the evidence and produced evidence summaries following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. GRADE evidence profiles and evidence-to-decision frameworks were created and used by the Guideline Development Group to make recommendations. This guideline was peer reviewed by an external group and approved by the WHO Guidelines Review Committee.

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RECOMMENDATIONS

These guidelines provide recommendations for the use of thermal ablation for the treatment of precancerous cervical lesions. These recommendations are applicable for women who have histologically confirmed CIN2-3 or for women who have been screened positive in a screen-and-treat strategy. These recommendations expand on the treatment for screen-and-treat strategies as provided in the WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention.

In these recommendations, the GDG decided to use the term thermal ablation instead of cold coagulation or thermocoagulation, to reflect the fact that it is an ablative treatment. The GDG decided that in these guidelines, as well as in future WHO publications, the term LLETZ will be used to represent a therapeutic intervention to excise the transformation zone (TZ). LLETZ is the original terminology used for excision of the TZ. The C4GEP manual, as well as some countries, use the term LEEP (Loop Electro Excision Procedure) and the two terms (LLETZ and LEEP) are often used interchangeably. The term LEEP also refers to a diagnostic procedure, requiring up to 2 cm of tissue to be excised from the cervix for the pathologist to make an accurate diagnosis.

ELIGIBILITY FOR THERMAL ABLATION AND CRYOTHERAPY

Eligibility for treatment should be assessed by colposcopy (if available) or by naked eye examination of cervix after applying 3–5% acetic acid for 1 minute.

Clinicians usually describe what they see when performing visual inspection (for example, if the TZ is fully visible; if the whole lesion is visible; if the lesion extends into the endocervix), and then consider if the probe can reach the whole lesion. Clinicians can consider using the International Federation for Cervical Pathology and Colposcopy's classification of three types of Transformation Zone, characterised by the size and site:

- A type 1 TZ is completely ectocervical and is therefore fully visible.
- A type 2 TZ is partially endocervical but is still fully visible. It may be shallow and within range of an ablative probe or may extend beyond reach of an ablative probe.
- A type 3 TZ extends out of view up the endocervical canal, i.e., the squamocolumnar junction (SCJ), and is not fully visible.

Following assessment as described above, women who screen positive, but there is no suspicion of invasive or glandular disease, (i.e. adenocarcinoma or adenocarcinoma in situ), are eligible for ablative therapy if:

- the TZ is fully visible, the whole lesion is visible and it does not extend into the endocervix, or
- the lesion is type 1 TZ; or
- the lesion is type 2 TZ where the probe tip will achieve complete ablation of the SCJ epithelium, i.e., where it can reach the upper limit of the TZ. Sometimes the SCJ can be seen high in the canal but a probe tip would not reach it.

Women who screen positive are not eligible for ablative therapy if there is any suspicion of invasive or glandular disease, (i.e. adenocarcinoma or adenocarcinoma in situ), and:

- the TZ is not fully visible because it is endocervical (Type 3 TZ); or
- it is a Type 2 TZ where the SCJ is out of reach of the probe tip.

INTERVALS FOR FOLLOW-UP

Intervals for follow-up should be conducted according to the WHO guidelines for treatment of cervical intraepithelial neoplasia 2–3 and adenocarcinoma in situ[1], and the WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention[2]. According to those recommendations, all women who have received treatment should receive post-treatment follow-up at 1 year to ensure effectiveness of treatment. Post treatment follow-up is critical, in particular for women living with HIV or women of unknown HIV status in areas with high endemic HIV infection.

[1] http://apps.who.int/iris/bitstream/10665/104174/1/9789241506779_eng.pdf?ua=1
[2] https://www.who.int/iris/bitstream/10665/94830/1/9789241548694_eng.pdf?ua=1

Recommendations	Strength of recommendation and certainty of evidence
Recommendation 1.a WHO suggests either LLETZ, or cryotherapy or thermal ablation to treat all women who have histologically confirmed CIN2+ disease and who are eligible for thermal ablation or cryotherapy. ***Remarks:*** The choice of LLETZ, or cryotherapy or thermal ablation depends on the expertise, training, equipment and consumables available, infrastructure and resources in a programme. This recommendation applies to all women, including women living with HIV. See Figure 1.	Conditional recommendation, moderate certainty in evidence of effects
Recommendation 1.b WHO suggests thermal ablation be provided at a minimum of 100 °C for 20–30 seconds using as many applications as needed to cover the entire transformation zone in overlapping fields.	Conditional recommendation, very low certainty in evidence of effects
Recommendation 2 In exceptional conditions when LLETZ is not available for women who have histologically confirmed CIN2+ disease and are not eligible for cryotherapy or thermal ablation, the GDG recommends an alternative treatment. The choice of alternative treatment will be dependent on the skills and resources available and referral to a higher level of care where a cone biopsy, trachelectomy or hysterectomy can be performed. ***Remarks:*** This recommendation applies to all women including women living with HIV. See Figure 1.	Strong recommendation, very low certainty in evidence of effects
Recommendation 3 WHO suggests providing either thermal ablation or cryotherapy to women screened positive with hrHPV or visual inspection with acetic acid (VIA); or hrHPV followed by VIA and who are eligible for ablative treatment, or providing LLETZ when the woman is not eligible for cryotherapy or thermal ablation. ***Remarks:*** This recommendation applies to all women, including women living with HIV. The choice of screening tests is based on WHO recommendations for screening and treatment. See Figure 2.	Conditional recommendation, very low certainty in evidence of effects
Recommendation 4 WHO suggests that prophylactic antibiotics are not used when providing thermal ablation.	Conditional recommendation, very low certainty in evidence of effects
Recommendation 5 WHO suggests that trained nurses, midwives or health care workers as well as physicians may perform thermal ablation in order to ensure the availability and accessibility of treatment.	Conditional recommendation, very low certainty in evidence of effects
Recommendation 6 In settings where LLETZ is available and accessible, WHO suggests LLETZ rather than thermal ablation or cryotherapy for women who test positive for cervical cancer after prior thermal ablation or cryotherapy. In settings where LLETZ is unavailable or inaccessible, the WHO recommends thermal ablation or cryotherapy rather than no treatment for women who test positive after prior thermal ablation or cryotherapy. ***Remarks:*** This recommendation is consistent with the recommendation to provide LLETZ after prior cryotherapy.	Conditional recommendation, very low certainty in evidence of effects Strong recommendation, very low certainty in evidence of effects

Figure 1a: Flowchart for histologically confirmed CIN2+

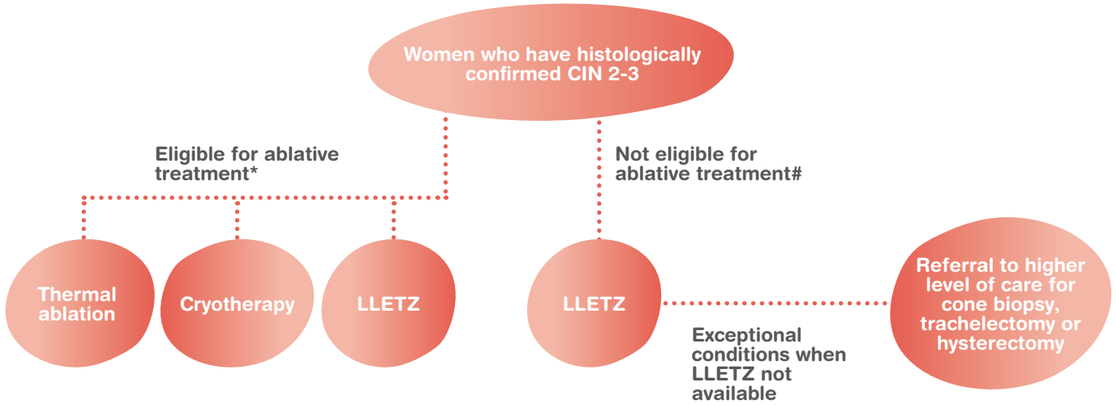
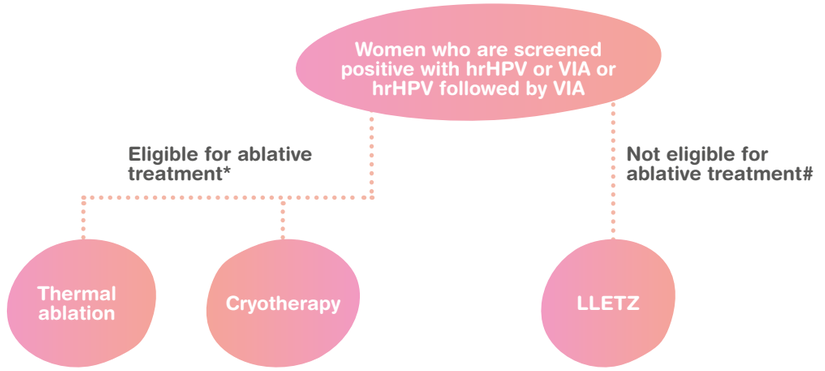


Figure 1b: Flowchart for screen positive with hrHPV or VIA or hrHPV followed by VIA



* Women who screen positive, but there is no suspicion of invasive or glandular disease, (i.e. adenocarcinoma or adenocarcinoma in situ), are eligible for ablative therapy if

- the TZ is fully visible, the whole lesion is visible and it does not extend into the endocervix, or
- the lesion is type 1 TZ, or
- the lesion is type 2 TZ where the probe tip will achieve complete ablation of the SCI epithelium, i.e., where it can reach the upper limit of the TZ. Sometimes the SCJ can be seen high in the canal but a probe tip would not reach it.

\# Women who screen positive are not eligible for ablative therapy if there is any suspicion of invasive or glandular disease, (i.e. adenocarcinoma or adenocarcinoma in situ), and

- the TZ is not fully visible because is endocervical (Type 3TZ), or
- is a Type 2 TZ where the SCJ is out of reach the probe tip.

1. INTRODUCTION

1.1 BACKGROUND

It is estimated that more than 311 000 women die of cervical cancer each year, and that 91% of these deaths occur in low- and middle-income parts of the world *(1)*. Demographic changes, ageing and lack of action mean that the number of deaths per year is projected to reach 460 000 by 2040 *(2)*. The highest burden is found in sub-Saharan Africa, Central and South America, East Africa, South and South-East Asia, and the Western Pacific.[3]

Screening programmes have dramatically reduced cervical cancer rates in high-income countries. In the United States of America (USA), for example, mortality has been reduced by 80% in 50 years thanks to screening by the Papanicolaou (PAP) smear test and treatment of confirmed precancerous cervical intraepithelial lesions grade 2 or more (CIN2+ *(2)*. Screening using the same cytology-based method and histological confirmation of lesions has not been so successful in low- and middle-income countries (LMIC), mainly because of high costs and logistical considerations specific to the PAP smear test, general lack of colposcopy and histology services, and inadequate access to treatment of precancerous lesions in these regions *(3)*.

Alternative tests have been introduced - first the visual inspection with acetic acid (VIA), and more recently, a nucleic acid test for human papillomavirus (HPV). Due to the lack of services for diagnostic confirmation, the first edition of the *WHO Comprehensive cervical cancer control: a guide to essential practice* (C4GEP) in 2006 recommends the implementation of screen-and–treat algorithms where women who are positive for a screening test are treated with ablative treatment (destruction of the cervical transformation zone, including the lesion). More recently, WHO has endorsed the use of cryotherapy through an evidence-based review in 2011 and in 2014 *(4,5)*, and in the WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention and the updated C4-GEP review of 2014 *(6,7)*. Cryotherapy was found to have similar efficacy compared to excision of the CIN2+ lesion by large loop excision of the transformation zone (LLETZ). WHO also published a technical specifications document for cryosurgical equipment *(8)*.

One major disadvantage of cryotherapy is the need for a refrigerant gas (N_2O or CO_2). The gas containers are bulky and heavy transport and the gas is not always easily available in low- and middle-income countries (LMICs) *(9)*. In addition, cryotherapy can be costly: the purchase of can be expensive, alongside the purchase or rental of the tank. It has been reported that this can lead to delay and even lack of treatment after a positive screening test, which undermines prevention through a screen-and-treat approach. Novel ablative treatment methods have been developed since the last update of the C4GEP (9), for which member countries and key stakeholders have approached WHO for guidance on their use. To overcome the need for cryo-gas, companies have developed portable devices that use electricity to cool the treatment probe to freezing point. This technology is used in some new devices like the CryoPenTM (by Cryopen Inc.). The system consists of a hand-held copper tip that is inserted into a refrigeration unit, and reusable tips. The entire system weighs about 10 kg. There is also a device (Cryopop) that uses gas more efficiently by converting the gas into a solid in order to freeze tissue. It will be established whether these devices comply with the WHO technical specifications for cryotherapy equipment *(8)*.

Thermal ablation is another novel ablative treatment for CIN, and is sometimes called “cold coagulation” or “thermocoagulation”. WHO and the Guideline Development group decided to use the term thermal ablation, as it describes most closely what the treatment is. The equipment is fairly simple and treatment is based on a 20–30 second application of a reusable metallic probe that is electrically heated to approximately 100 °C, leading to epithelial and stromal destruction of the lesion. Conventional desktop devices weigh about 5 kg and are reasonably portable. Newer handheld, battery-operated devices weigh less than 2 kg, and are compact enough to carry in a backpack which makes for easy implementation in LMIC. The treatment time is shorter with thermal ablation. As in the case of cryotherapy,

[3] Globocan 2019

thermal ablation is provided by a variety of qualified health care personnel, including primary health care workers, and no anesthesia is required.

1.2 RATIONALE FOR RECOMMENDATIONS

Thermal ablation is currently not included in the latest version of the WHO guidelines for screening and treatment of precancerous lesions for cervical cancer, or WHO guidelines for treatment of cervical intraepithelial neoplasia 2–3 and adenocarcinoma in situ *(5,6)*. Although the technique was used quite frequently in the UK in the 1980s and early 1990s, there were few reports on its use. Hence WHO concluded at that time that there were insufficient efficacy and safety data to develop recommendations on its use at the time of the last revision of the C4GEP. However, evidence is now accumulating and has been synthesized in a meta-analysis that has now been updated *(10)*.

1.3 OBJECTIVES

The objectives of these guidelines are

- to provide evidence-based guidance on the use of thermal ablation for cervical precancer; and,
- to support countries in updating their national guidelines for the use of thermal ablation for cervical precancer.

1.4 TARGET AUDIENCE

This document is intended primarily for policy-makers, managers, programme officers, and other professionals in the health sector who have responsibility for choosing strategies for cervical cancer prevention and control, at country, regional, and district levels. Individuals working in reproductive health care programmes, particularly programmes for prevention of sexually transmitted infections including HIV/AIDS and for family planning, at the district and primary health care levels, should also consult this document to understand how recommendations are developed and why it is vitally important to select and implement evidence-based strategies to prevent cervical cancer. Technical terms used in the document are defined in the Glossary.

This document is intended primarily for policymakers, managers, programme officers, and other professionals in the health sector

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2. METHODS

These guidelines were developed following the methods outlined in the 2014 edition of the *WHO handbook for guideline development (11)*.

2.1 GUIDELINE DEVELOPMENT GROUP (GDG)

The GDG was established with 35 members who brought varied expertise in technical and societal aspects of screening and treatment of precancerous lesions (Annex A). Members were from the African Region, Region of the Americas, South-East Asia Region, European Region, and the Western Pacific Region. The GDG participated in in-person meetings and teleconferences to identify and prioritize questions to be addressed in this guideline, to discuss the evidence reviews, and to make recommendations. The GDG reviewed and approved the final version of this guideline.

2.2 QUESTIONS AND OUTCOMES

In April 2017, the GDG discussed the approach to develop the questions for this review based on the population, intervention, comparison and outcome framework (PICO). It was proposed to follow a similar set of recommendation questions from the 2011 cryotherapy guidelines *(4)*. The GDG agreed that recommendations should be made about the use of thermal ablation for the treatment of precancerous cervical lesions and about its use in screen-and-treat strategies. The group also agreed that evidence would be needed to inform the specific application of thermal ablation in practice, for example, in key populations, by specific health care professionals, and with specific modalities of use. PICO questions specific to thermal ablation were then prepared by the WHO secretariat in collaboration with the systematic review team and shared with the GDG. A final list of PICO questions was agreed upon during a teleconference with the GDG in September 2017 (Annex B).

The outcomes previously identified for the guidelines for treatment of precancerous lesions and screen-and-treat strategies to prevent cervical cancer *(5, 6)* were used as a basis for discussion by the GDG. The thermal ablation GDG reviewed and agreed upon the outcomes to use in this guideline via email and a teleconference call. The outcomes are included in the PICO questions in Annex B.

2.3 REVIEWS OF THE EVIDENCE

We used a hierarchical approach to search for evidence to make recommendations. We searched for systematic reviews, then primary studies when no systematic reviews were available. We used the evidence from a recently published systematic review and meta-analysis for the benefits and harms of thermal ablation that included studies in which at least one group of women received thermal ablation *(10)*. Randall and colleagues *(10)* conducted a comprehensive search of multiple databases up to December 2017 and reviewed references of included studies. We also searched for information about patient values and preferences, resources, acceptability, equity and feasibility related to thermal ablation from 1997 up to January 2018. We updated the search for the systematic reviews conducted for the WHO guidelines for treatment of cervical intraepithelial neoplasia 2–3 and adenocarcinoma in situ for cryotherapy for studies greater than 300 people since it was unlikely that studies of fewer than 300 people would change the previously calculated pooled proportions *(12)*. The search was conducted from 2012 to January 2018, but no new studies meeting the eligibility criteria were identified. We obtained preliminary data from the GDG for four ongoing or completed, but not yet published, studies in India, Peru and El Salvador, Zambia, South Africa. We also used the test accuracy data from the systematic review and meta-analysis for the WHO guidelines for screen-and-treat strategies to prevent cervical cancer by Mustafa and colleagues *(13)*. This search was conducted up to September 2012 and was not updated. The results were compared to field accuracy of the screening tests.

When there was little evidence available, we systematically obtained the observations of the GDG using a survey (www.surveymonkey.com). Questions in the survey were related to the modality of thermal ablation used, such as

timing of application, shape of probe, and temperature of probes (Annex C).

Two members of the systematic review team screened studies independently, and extracted and assessed the risk of bias of the individual studies using a tool specific to the study design (e.g. Cochrane Risk of Bias Tool for randomized controlled trials (www.handbook-5-1.cochrane.org) or used the risk of bias assessment in the published systematic reviews when available. We used the pooled analyses from systematic reviews when available. However, when not available, one member of the team synthesized the data quantitatively in RevMan 5.2 (https://community.cochrane.org/help/tools-and-software/revman-5) or narratively, and another member of the team verified the analyses. For dichotomous outcomes, we calculated a risk ratio with 95% confidence intervals by pooling results from randomized studies or pooling results from non-randomized studies with two groups using the random effects model. Effects were converted to absolute effects using the calculated relative effect and a representative baseline risk, typically the pooled proportion of the event without the treatment across studies. When studies with one group receiving an intervention were included (e.g., case series), a pooled proportion of an event (and confidence intervals) was calculated across the studies using the generic inverse variance. For continuous outcomes, a mean difference or a standardized mean difference (when studies used different scales to measure an outcome) was calculated.

For screen-and-treat recommendations, outcome data were not available from randomized or non-randomized studies. We therefore used the same model that was developed to make the recommendations for screen-and-treat strategies to prevent cervical cancer *(6)*. We used an Excel spreadsheet to

The certainty of the evidence is assessed at four levels in the GRADE approach:

- High – we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate – we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low – our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low – we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.

2.4 MAKING RECOMMENDATIONS

Recommendations were developed during four teleconference meetings with the GDG. The methodologist presented the evidence-to-decision frameworks during the meetings (completed evidence-to-decision frameworks are in Annex D and the evidence reviews are in Annex E). When formulating the recommendations, the GDG considered and discussed the desirable and undesirable effects of the interventions, the value placed on the outcomes, the associated costs and use of resources, the acceptability of the interventions to all stakeholders, the impact on health equity, and the feasibility of implementation. Judgements were made for each criterion above, and guideline recommendations were agreed. The goal was to reach consensus across the GDG. Disagreements among the GDG members were noted in the evidence-to-decision framework for each judgement. In the case of failure to reach consensus for a recommendation, the planned procedure was

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Table 1. Implications of strong and conditional recommendations

Implications	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with the individual's values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences.
For policy-makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

According to the GRADE approach, the strength of each recommendation was rated as either strong or conditional. Strong recommendations were made when all the desirable consequences of treatment outweighed the undesirable consequences, and are presented using the wording "recommends". Conditional recommendations were made when the desirable consequences probably outweighed the undesirable consequences, and are worded as "suggests". The implications of the different strengths of recommendations for patients, clinicians and policy-makers are explained in detail in Table 1.

2.5 MANAGEMENT OF CONFLICTS OF INTEREST

We followed the WHO guidelines for declaration of interests (DOI) *(14)*. We obtained DOI statements from all GDG members prior to the guideline meetings, and members had to disclose any changes to their interests at the beginning of each meeting. We also updated their DOI statements before the publication of these guidelines. Three experts of the GDG participated in clinical trials on ablative treatment, but it was not assessed as a barrier to participating in the meetings and discussions. The WHO Secretariat concluded that there were no significant conflicts of interest that would exclude any member from participating fully in the guideline development process (see Annex A). Therefore, options for conditional participation, partial or total exclusion of any GDG member were not necessary.