

Table of Contents

	Executive Summary	XXIII
1	Introduction	1
1.1	Burden of cervix cancer in the EU	3
1.2	Cervical cancer and screening	4
1.3	Cause of cervical cancer	4
1.4	European policy: Council Recommendation of 2 December 2003 on Cancer Screening	4
1.5	First edition of the European Guidelines for Quality Assurance in Cervical Cancer Screening	5
1.6	Content of the second guideline edition	5
1.7	The future	6
1.8	Acknowledgements	7
1.9	References	7
2	Epidemiological Guidelines for Quality Assurance in Cervical Cancer Screening	11
2.1	Executive summary	13
2.2	Introduction	14
2.3	Epidemiology of cervical cancer	15
2.3.1	Burden of disease	15
2.3.1.1	Current incidence and mortality of cervical cancer	15
2.3.1.2	Trends	15
2.3.1.3	Survival	19
2.3.2	Natural history of disease	20
2.3.3	Risk factors	21
2.3.4	Evidence for efficacy and effectiveness of cytological screening	21
2.3.4.1	Age group to be targeted	22
2.3.4.2	Screening interval	22
2.3.4.3	Screening modality: organized vs. opportunistic screening	22
2.4	Organization of cervical cancer screening	25
2.4.1	Principles of the determination of a screening policy	25
2.4.1.1	Decision to run a screening programme	25
2.4.1.2	European screening policy	25
2.4.2	Integration within the healthcare system	27
2.4.2.1	Defining target population and relevant health-care professionals and facilities	30
2.4.2.2	Inventory of baseline conditions	32

TABLE OF CONTENTS

2.4.3	Invitation and attendance	34
2.4.3.1	How to reach the target population and increase coverage	34
2.4.4	Screening test and management of screen-positive women	35
2.4.4.1	Smear taking	35
2.4.4.2	Smear interpretation and reporting	36
2.4.4.3	Management of screen-positive women	36
2.4.4.4	Colposcopy and treatment	36
2.4.5	Health information systems and registration	37
2.4.5.1	Registration of the screening programme	38
2.4.5.2	Data collection from opportunistic smears	38
2.4.5.3	Registration of cervical cancers	39
2.4.5.4	Storage of biological materials	39
2.4.6	Legal and ethical aspects of data collection and linkage	39
2.5	Monitoring and evaluation	41
2.5.1	Screening outcome	41
2.5.2	Monitoring	44
2.5.3	Auditing screening histories of cancer cases	45
2.5.4	Cost-effectiveness	46
2.6	References	47
Annex	Tables	53
3	Methods for Screening and Diagnosis	69
3.1	Executive summary	71
3.2	Assessment of the performance of screening tests: principles and criteria	73
3.3	Conventional cervical cytology	77
3.3.1	Description of conventional cervical cytology	77
3.3.1.1	Principles of conventional cytology	77
3.3.1.2	Reading a cervical smear	77
3.3.1.3	Screening technique and localization	77
3.3.1.4	Cytological interpretation and reporting	78
3.3.1.5	Clinical applications of cervical cytology	78
3.3.1.6	Quality of conventional smears	78
3.3.2	Performance of conventional cervical cytology	78
3.4	Liquid-based cytology	80
3.4.1	Description	80
3.4.2	Rationale for liquid-based cytology	81
3.4.3	Recent reviews, meta-analyses and pilot studies	82
3.4.3.1	Comparison of the test characteristics of liquid-based cytology with the conventional Pap-smear	82
3.4.3.2	Comparison of the adequacy of liquid-based and conventional smears	84
3.4.3.3	Pilot projects conducted in Scotland and England	84
3.4.3.4	Influencing factors	85

TABLE OF CONTENTS

3.4.3.5	Economical aspects of liquid-based cytology	85
3.4.3.6	Training and time-trend effects	85
3.4.4	Recommendations for future research	86
3.4.5	Conclusions	86
3.5	Quality of the cervical smear	87
3.6	Automated cytological screening	88
3.6.1	Description of automated screening devices	88
3.6.2	Rationale for automated screening	89
3.6.3	Evaluation of performance	89
3.6.4	Conclusion	91
3.7	Colposcopy	91
3.7.1	Description	91
3.7.2	Accuracy of colposcopy	92
3.7.3	Conclusions	93
3.8	HPV DNA detection	93
3.8.1	Introduction	93
3.8.2	HPV nucleic acid detection systems	93
3.8.2.1	Hybrid Capture 2	93
3.8.2.2	General primer PCR based on the primer pair GP5+/GP6+	94
3.8.2.3	General primer MY09/11 system	94
3.8.2.4	SPF10 PCR	95
3.8.2.5	Amplicor Human Papillomavirus Test	95
3.8.2.6	Real time PCR	95
3.8.2.7	HPV DNA typing methods	95
3.8.2.8	DNA micro-array chips	96
3.8.2.9	Detection of viral oncogene transcripts	96
3.8.2.10	Conclusion	97
3.8.3	Use of HPV testing in primary screening	97
3.8.3.1	Cross-sectional accuracy	97
3.8.3.2	Age groups to be targeted and screening intervals for HPV screening programs	99
3.8.3.3	Possible strategies to improve the specificity of HPV testing for primary screening	101
3.8.3.4	Follow-up and longitudinal performance	102
3.8.3.5	What types of studies are necessary and what should their endpoint be?	102
3.8.3.6	Ongoing European randomized trials	104
3.8.3.7	Using cost-effectiveness modeling to design HPV screening programs	104
3.8.4	Use of HPV testing in triaging women with equivocal smears	105
3.8.5	Use of HPV testing in triaging women with LSIL	107
3.8.6	Use of HPV testing in follow-up after treatment of CIN	109
3.9	Conclusions	111
3.10	References	112
Annex 1	Collection of cellular material of the uterine cervix, Preparation of an adequate Pap smear	129
Annex 2	Recommendations for cervical cytology terminology	141

4	Laboratory Guidelines and Quality Assurance Practices for Cytology	153
4.1	Executive summary	155
4.2	Introduction	155
4.3	Personnel and organization	155
4.3.1	General	155
4.3.2	Requirements for cyto-technologists	156
4.3.2.1	Cyto-technologist	156
4.3.2.2	Senior cyto-technologist	156
4.3.3	Requirements for other technical laboratory personnel	158
4.3.4	Requirements for a cyto-pathologist	158
4.3.5	Requirements for administrative personnel	158
4.3.6	Final responsibility	158
4.4	Material requirements	159
4.4.1	Buildings, rooms and furniture	159
4.4.2	Equipment for staining, microscopes, record systems and teaching materials	159
4.5	Handling and analysis of cervical samples	160
4.5.1	Laboratory preparation	160
4.5.2	Assessment of the sample: stepwise screening	160
4.5.2.1	Initial assessment	160
4.5.2.2	Samples qualifying for a second screening assessment	161
4.5.3	Workload requirements – primary screening	161
4.5.4	Archiving	161
4.6	Recording of results	162
4.6.1	Laboratory information system	162
4.6.2	Authorization of results	163
4.6.3	Laboratory response time	163
4.7	Quality management	163
4.7.1	Internal quality management	163
4.7.1.1	Laboratory quality management (preanalytical quality management)	163
4.7.1.2	Analytical quality management (cytology)	164
4.7.1.3	Internal continuing education	167
4.7.2	External quality management	167
4.7.2.1	External continuing education	167
4.7.2.2	External quality control of screening skills	167
4.7.2.3	Accreditation of the laboratory unit	168
4.7.3	Responsibilities for quality control	169
4.8	Communication	169
4.8.1	Other laboratories	169
4.8.2	General practitioners, gynaecologists and other sample-takers	169
4.8.3	Health authorities	169
4.8.4	Patients	169
4.9	References	170

5	Techniques and Quality Assurance Guidelines for Histopathology	173
5.1	Executive summary	175
5.2	Introduction	175
5.3	Punch biopsies	176
5.3.1	Diagnostic goal	176
5.3.2	Macroscopic description	176
5.3.3	Technique	176
5.3.4	Histological diagnosis	176
5.4	Excision biopsies	178
5.4.1	Diagnostic goals	178
5.4.2	Macroscopic description	178
5.4.3	Technique	178
5.4.4	Histological diagnosis	179
5.5	Endo-cervical curettage (ECC)	180
5.5.1	Diagnostic goal	180
5.5.2	Macroscopic description	181
5.5.3	Technique	181
5.5.4	Histological diagnosis	181
5.6	Immunohistochemistry	181
5.7	Data collection	182
5.8	Quality assurance	183
5.9	References	187
6	Management of Abnormal Cervical Cytology	191
6.1	Executive summary	193
6.2	Introduction	193
6.3	Diagnostic evaluation of the abnormal smear	194
6.3.1	Repeat cytology	194
6.3.2	HPV testing	194
6.3.3	Colposcopy	195
6.3.3.1	The transformation zone	195
6.3.3.2	Technique of colposcopy	195
6.3.3.3	Colposcopic features suggestive of CIN	196
6.3.3.4	Colposcopic terminology	197
6.3.3.5	The new transformation zone classification	199
6.3.3.6	Diagnostic accuracy of colposcopy	200
6.3.3.7	Colposcopic examination of the vagina and vulva	200
6.3.3.8	Colposcopy of the post-menopausal cervix	201
6.3.3.9	Colposcopy in pregnancy and in the post partum period	201
6.3.3.10	Conclusions for colposcopy	201

TABLE OF CONTENTS

6.3.4	Cervical biopsy	202
6.3.5	Endo-cervical curettage	202
6.4	Treatment procedures	203
6.4.1	Excision of the lesion	203
6.4.2	Local destructive therapy	204
6.5	Management of patients according to the severity of cytological abnormalities	205
6.5.1	Management of women with atypical squamous cells of undetermined significance	206
6.5.1.1	Data providing evidence	206
6.5.1.2	Management options in case of ASCUS	206
6.5.1.3	Management of ASC-H	207
6.5.2	Management of women with LSIL	207
6.5.2.1	Data providing evidence	207
6.5.2.2	Management options in case of LSIL	208
6.5.3	Management of women with HSIL	208
6.5.3.1	Data providing evidence	208
6.5.3.2	Management options in case of HSIL	209
6.5.4	Management of women with glandular cytological abnormality	209
6.5.4.1	Data providing evidence	209
6.5.4.2	Management options in case of glandular lesions	210
6.5.5	Management of cervical smears showing endometrial cells	210
6.6	Management of histologically confirmed CIN	211
6.6.1	Management of CIN1	211
6.6.2	Management of CIN2 and CIN3	212
6.6.3	Micro-invasive cancer	212
6.7	Complications after treatment of CIN	213
6.8	Follow-up after treatment of CIN	213
6.8.1	Significance of involved margins in the excised specimen	214
6.8.2	The role of HPV testing in follow-up after treatment	214
6.8.3	Treatment of residual and recurrent lesions	215
6.9	Management of women in other clinical situations	215
6.9.1	Management of women with cytological abnormality in pregnancy	215
6.9.2	Adolescent women	216
6.9.3	Post menopausal women	216
6.9.4	Hysterectomised women	216
6.9.5	Immuno-suppressed patients	217
6.9.6	HIV-positive women	217
6.9.7	Procedure in case of cyto-colposcopic discrepancies	218
6.10	Quality assurance of patient management	218
6.11	Measures to improve follow-up	219
6.11.1	Fail-safe measures to assure compliance with follow advice	219
6.11.2	Correlation of cytology findings with the final histological diagnosis	219
6.12	Patient information	220

TABLE OF CONTENTS

6.13	Data collection on treatment and follow up of screen-detected lesions	220
6.14	References	222
7	Key Performance Indicators	233
7.1	Executive summary	235
7.2	Screening intensity	235
7.3	Screening test performance	236
7.4	Diagnostic assessment and treatment	237
7.5	Definition of performance parameters in cervical cancer screening	238
7.5.1	Screening intensity	239
7.5.2	Screening test performance	241
7.5.3	Diagnostic assessment and treatment	243
Annexes		
Chapter 2		53
Annex	A Tables	Characteristics of the screening programme
		55
	B Tables	Annual tabulations utilizing individual screening data
		57
Chapter 3		
Annex 1	Collection of cellular material of the uterine cervix	129
	Preparation of an adequate Pap smear	
	1.1	Introduction
		131
	1.2	Facilities
		131
	1.3	Preparing to take the sample
		132
	1.4	Sampling the transformation zone
		132
	1.4.1	Sampling devices
		133
	1.4.2	Sampling and preparing a conventional smear
		134
	1.4.2.1	Cervical broom
		134
	1.4.2.2	Combination of spatula and endocervical brush
		135
	1.4.2.3	Sampling with the extended tip spatula alone
		136
	1.4.3	Preparing a liquid-based cytology sample
		136
	1.4.4	Completing sampling
		137
	1.5	Transport to the laboratory
		138
	1.6	Feedback on the quality of the specimen
		138

TABLE OF CONTENTS

	1.7	References	138
Annex 2		Recommendations for cervical cytology terminology	141
	2.1	Introduction	143
	2.2	Specimen adequacy	143
	2.3	General categorization	143
	2.4	Interpretation/result	144
	2.4.1	Negative for intraepithelial lesion or malignancy	144
	2.4.2	Cells indicating a squamous intraepithelial lesion/neoplasia/ dysplasia	144
	2.4.2.1	LSIL, mild dysplasia, cellular changes suggesting CIN1	144
	2.4.2.2	HSIL, cellular changes suggesting CIN2 / moderate dysplasia	145
	2.4.2.3	HSIL, cellular changes suggesting CIN3 / severe dysplasia / carcinoma in situ	145
	2.4.2.4	Invasive squamous cell carcinoma	145
	2.4.2.5	Atypical / borderline squamous cells	145
	2.4.2.6	Atypical squamous cells – high-grade not excluded (ASC-H)	145
	2.4.3	Glandular cell abnormalities	146
	2.4.3.1	Endocervical adenocarcinoma in situ	146
	2.4.3.2	Adenocarcinoma	146
	2.4.3.3	Atypical / borderline changes in glandular cells	146
	2.4.4	Other Cellular changes	147
	2.5	Additional remarks	147
	2.5.1	Automated review	147
	2.5.2	Ancillary testing	147
	2.5.3	Educational notes and suggestions	147
	2.6	Summary	147
	2.7	References	150
 Appendices			
Appendix 1		Guidance on Communication with women and health professionals involved in cervical cancer screening	245
Appendix 2		HPV vaccination – An overview	271
		Glossary of terms	283
		List of abbreviations	289