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Evidence-based Series 1-6 EDUCATION AND INFORMATION 2010

Epirubicin, as a Single Agent or in Combination, for Metastatic Breast Cancer

Members of the Breast Cancer Disease Site Group
and the Systemic Treatment Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

A review conducted in 2010 put Evidence-based Series (EBS) 1-6 in the Education and Information Section. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardize process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Evidence-based Series (EBS) consists of the following 4 parts:

1. **Guideline Overview**
2. **Summary**
3. **Full Report**
4. **Document Assessment and Review Tool**

and is available on the CCO website (http://www.cancercare.on.ca)
PEBC Breast Cancer Disease Site Group page at:
http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs/.

Release Date: September 15, 2011

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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Evidence-based Series 1-6 EDUCATION AND INFORMATION 2010

Epirubicin, as a Single Agent or in Combination, for Metastatic Breast Cancer

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version Mar 1997	1966 to 1996	Full Report	Web publication	Not Applicable
Updated Feb 2002	1996 to 2002	New data added to original Full Report	Updated Web publication	Most recent search done in Apr 2003
Reviewed Version Jun 2010	Document Assessment and Review Tool		Updated Web publication	Guideline ARCHIVED

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Evidence-based Series 1-6 ARCHIVED 2010

Epirubicin, as a Single Agent or in Combination, for Metastatic Breast Cancer

Guideline Review Summary

Review Date: June 11, 2010

The 2002 guideline recommendations are

ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

OVERVIEW

Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO) in 1998 and the first update released in February 2002. In June 2010, the PEBC guideline update strategy was applied, and the recommendations were archived. The Summary and the Full Report in this review are the same as in the February 2002 version.

Update Strategy

The PEBC update strategy includes an updated search of the literature, the review and interpretation of new eligible evidence by the clinical experts from the authoring panel and consideration of the guideline and its recommendations based on the new available evidence. (Please see the Document Assessment and Review Tool at the end of this document.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

What is the effectiveness of epirubicin, compared with doxorubicin, in patients with metastatic breast cancer?

Literature Search and New Evidence

A search for new literature with respect to this question was not conducted as it was determined that the recommendations regarding this question are no longer relevant. The guideline and its recommendations have been ARCHIVED.

Impact on Guidelines and Its Recommendations

The Breast Cancer DSG **ARCHIVED** the 2003 recommendations. Therefore this guideline will no longer be maintained.

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Epirubicin, as a Single Agent or in Combination, for Metastatic Breast Cancer

Practice Guideline Report # 1-6

B.P. Findlay, C. Walker-Dilks, K. Pritchard, and members of the Breast Cancer Disease Site Group and the Systemic Treatment Disease Site Group

Please see the EBS 1-6 Archived 2011 Guideline Review Summary and the Document Assessment and Review Tool for the summary of updated evidence published between 2002 and 2010

Report Date: April 30, 2003

SUMMARY

Guideline Question
What is the effectiveness of epirubicin, compared with doxorubicin, in patients with metastatic breast cancer?

Target Population
Women with metastatic breast cancer.

Recommendations
Epirubicin, at doses equivalent to doxorubicin, has been shown to be equally efficacious and less toxic than doxorubicin. Doxorubicin, however, is an acceptable alternative.

Methods
Entries to MEDLINE (1966-April 2003), the Cochrane Library (Issue 1, 2003), and abstracts published in conference proceedings were searched for evidence relevant to this practice guideline.

Evidence was selected and reviewed by members of the Practice Guideline Initiative's Breast Cancer Disease Site Group. This practice guideline has been reviewed and approved by the Breast Cancer Disease Site Group, which is comprised of surgeons, medical oncologists, epidemiologists, a pathologist, a medical sociologist, and a patient representative.

External review of the original practice guideline report by Ontario practitioners was obtained through a mailed survey. Final approval of the original guideline was obtained from the Practice Guidelines Coordinating Committee. The Practice Guideline Initiative has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature and where appropriate, integration of this literature with the original guideline information.

Key Evidence

- Seven randomized trials comparing epirubicin and doxorubicin at equal doses (as single agents in three trials and as part of multi-agent chemotherapy in four trials) found no significant differences in tumour response rate or survival between these two agents. Survival data from published reports of five trials and response data for six trials were available for meta-analysis by the guideline developers. The meta-analysis did not detect differences in pooled one-year survival rates (risk ratio for mortality, 1.01; 95% confidence interval, 0.85 to 1.2; p=0.87) or response rate (risk ratio, 1.04; 95% confidence interval, 0.92 to 1.18; p=0.51).
- Five randomized trials comparing epirubicin at a higher dose to doxorubicin (as single agents in four trials and as part of multi-agent chemotherapy in one trial) detected no significant differences between these two agents in response rate or survival.
- Significantly higher response rates were observed with higher doses of epirubicin in five of six randomized trials that compared escalating doses of epirubicin (as a single agent in two trials and as part of multi-agent chemotherapy in four trials); no differences in survival were observed between doses.
- Less nausea and vomiting (risk ratio, 0.76; 95% confidence interval, 0.63 to 0.92; p=0.0048), neutropenia (risk ratio, 0.52; 95% confidence interval, 0.35 to 0.78; p=0.0017), and cardiac toxicity (risk ratio, 0.43; 95% confidence interval, 0.24 to 0.77; p=0.0044), including a trend towards fewer episodes of congestive heart failure (risk ratio, 0.38; 95% confidence interval, 0.14 to 1.04; p=0.059), were observed with epirubicin compared to doxorubicin.

For further information about this practice guideline, please contact:
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The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.
Visit http://www.cancercare.on.ca for all additional Practice Guidelines Initiative reports.

PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.[1] The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

For the most current versions of the guideline reports and information about the PEBC, please visit the CCO Web site at:
http://www.cancercare.on.ca
For more information, contact our office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775
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Disclaimer

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

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Epirubicin, as a Single Agent or in Combination, for Metastatic Breast Cancer

Practice Guideline Report # 1-6

B.P. Findlay, C. Walker-Dilks, K. Pritchard, and members of the Breast Cancer Disease Site Group and the Systemic Treatment Disease Site Group

Please see the EBS 1-6 Archived 2011 Guideline Review Summary and the Document Assessment and Review Tool for the summary of updated evidence published between 2002 and 2010.

Report Date: April 30, 2003

FULL REPORT

I. QUESTION

What is the effectiveness of epirubicin, compared with doxorubicin, in patients with metastatic breast cancer?

II. CHOICE OF TOPIC AND RATIONALE

Doxorubicin, regarded as being one of the most active chemotherapy agents for the treatment of breast cancer, is widely used. Epirubicin has been used more recently, because of evidence showing efficacy equivalent to that of doxorubicin but with less toxicity. In Ontario, considerable variation exists in the relative proportions of these two drugs used in different clinics. Together, they make up a significant proportion of money spent on chemotherapy. On a mg per mg basis, epirubicin is only slightly more expensive but, because of lower toxicity, it can be given in higher doses, leading to substantially higher costs. This guideline was written to provide a rationale for the choice between these two anthracycline agents and to make recommendations on the dose of epirubicin.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI), using the methods of the Practice Guidelines Development Cycle.[1] Evidence was selected and reviewed by members of the Breast Cancer Disease Site Group (DSG) and methodologists. Members of the Breast DSG disclosed potential conflict of interest information.

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the use of epirubicin in women with metastatic breast cancer, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

MEDLINE and CANCERLIT were searched (1985 to 1996) using the terms epirubicin, doxorubicin, and breast neoplasms. PDQ was searched for ongoing trials using the terms breast cancer and epirubicin.

Update

The literature search was revised to combine disease-specific text words and subject headings (breast, mammary, cancer, carcinoma, neoplasm[s]), treatment-specific terms (epirubicin, doxorubicin and adriamycin), and design-specific terms (meta-analysis, randomized controlled trial[s]). The literature search has been updated with the revised search terms using MEDLINE (through April 2003), the Cochrane Library (Issue 1, 2003), the Physician Data Query (PDQ) database, and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1997-2002) and the San Antonio Breast Cancer Symposium (2001-2002).

Inclusion Criteria

1. Articles were selected for inclusion in this systematic review of the evidence if they were randomized controlled trials comparing epirubicin with doxorubicin in metastatic breast cancer, either as single agents or in combination, and as either first- or second-line chemotherapy.
2. Trials were also selected if they compared different dosages of epirubicin.

Synthesizing the Evidence

In order to obtain a more precise assessment of the relative effects (on response rate, survival, and toxicity) of epirubicin versus doxorubicin, the results of the randomized trials of equal doses of these two agents were pooled using the software application *Metaanalyst*$^{0.988}$ provided by Dr. Joseph Lau, Tufts New England Medical Centre, Boston, MA. Results are expressed as risk ratios (95% confidence interval [CI]); estimates >1.0 favour doxorubicin and estimates <1.0 favour epirubicin for all variables. Data were analyzed using fixed-effects models when no significant heterogeneity was found among studies.

IV. RESULTS

Literature Search Results

Eleven published reports of randomized controlled trials and two reports available only in abstract form were selected as relevant to the topic. The studies are grouped according to dosage: 1) epirubicin and doxorubicin at equal doses, 2) epirubicin dose higher than doxorubicin, and 3) escalating doses of epirubicin. Study details are given in Tables 1a to 1c. For abbreviations, dosages, and schedules, see Appendix 1.

Update

All the known randomized trials comparing doxorubicin to epirubicin, or those comparing escalating doses of epirubicin, are summarized in Table 1u.

Table 1a: Randomized controlled trials comparing epirubicin and doxorubicin at equal doses.

Trial	Patients Evaluable	Treatment Allocation*	Response Rate (%) PR+CR ** (CR)	P value	Median Survival (months)	P value	Congestive Heart Failure (# patients)	Other Cardiac Toxicity (# patients)	Grade 3&4 Nausea and vomiting (% patients)	Grade 3&4 Neutropenia (% patients)
French (1)	113 117	FAC-50 FEC-50	52 (9) 50 (14)	NS	17 15	NS	3 0	5 0	13*** 8	5*** 2
Italian (2)	221 222	FAC-50 FEC-50	56 (15) 54 (11)	NS	20 19	NS	4 1	21 8	47 35	28 15
Lopez (3)	46 48	FAC-50 FEC-50	46 (16) 44 (12)	NS	16 14	NS	3 0	0 1	72 51	24 15
Heidemann (4)	51 66	AC-40 EC-40	42 (8) 42 (18)	NS	Data not available		0 1	4 3		
Lawton (5)	28 28	Adr-70 Epi-70	36 (7) 32 (0)	NS	~8 ~10	†	0 1	1 0	22 18	7*** 3
Gasparini (6)	21 22	Adr-20 Epi-20	33 (5) 36 (0)	NS	11 12	NS	1 0	3 2	5 0	5 0
Castiglione (7)	~50 ~50	Adr-20 Epi-20	29 28	NS	15 13	NS				

*Letters represent the treatment regimen, numbers represent the dose of doxorubicin or epirubicin in mg/m^2. See Appendix 1 for complete information on dosages and schedules.

FAC 5-fluorouracil, adriamycin (doxorubicin) and cyclophosphamide
FEC 5-fluorouracil, epirubicin and cyclophosphamide
AC Adriamycin (doxorubicin) and cyclophosphamide
EC Epirubicin and cyclophosphamide
Adr Adriamycin (doxorubicin)
Epi Epirubicin
** PR = partial response; CR = complete response
*** percentage of courses of treatment rather than patients
† Mortality hazard ratio (relative risk of death) favours epirubicin compared with doxorubicin [hazard ratio, 0.53; 95% CI, 0.3 to 0.94]

Table 1b. Randomized trials comparing epirubicin at a higher dose with doxorubicin.

Trial	Patients Evaluable	Treatment Allocation*	Response Rate(%) PR+CR **	(CR)	P value	Median Survival (months)	P value	Congestive Heart Failure (# patients)	Other Cardiac Toxicity (# patients)	Grade 3&4 Nausea and Vomiting (%)	Grade 3&4 Neutropenia (%)
Perez (8)	68	Adr-60	47	(13)	NS	12	NS	1	7	25	3
	72	Epi-90	49	(7)		10		2	5	32	3
Jain (9)	28	Adr-60	25	(0)	NS	NR	NS	5	NR	NR	20
	24	Epi-85	25	(0)		NR		4	NR	NR	18
Humblet (10)	~50	VAC-50	42	(13)	NS	14	NS	4	11	NR	NR
	~50	VEC-65	47	(10)		16		2	5	NR	NR
Update: February 2002											
EORTC (1u)	118	Adr-75	36	(4)	NS	12	NS	9	NR	32	NR
	114	Epi-90	28	(2)		11		2	NR	27	NR
Gundersen (2u)	81	Adr-20	36	(3)	NS	~14	NS	NR	NR	NR	NR
	68	Epi-50	22	(3)		~14		NR	NR	NR	NR

Table 1c. Randomized trials comparing escalating doses of epirubicin.

Trial	Patients Evaluable	Treatment Allocation*	Response Rate (%) PR+CR **	(CR)	P value	Median Survival (month)	P value	Congestive Heart Failure (# patients)	Other Cardiac Toxicity (# patients)	Grade 3&4 Nausea and Vomiting (%)	Grade 3&4 Neutropenia (%)
Focan (11)	71	FEC-50	41	(7)	<0.00	24	NS	0	6	NR	2
	70	FEC-100	69	(13)	1	27		0	5	NR	7
Habeshaw (12)	104	Epi-50	23	(4)	0.006	10	NS	0	2	15	3
	105	Epi-100	41	(10)		10		0	4	34	10
Bastholt (13)	75	Epi-40	20		< 0.01	13.6	NS	2	1	NR	NR
	66	Epi-60	19.7			14.0		1	2	NR	NR
	64	Epi-90	37.5			14.6		2	0	NR	NR
	58	Epi-135	36.2			11.3		0	0	NR	NR
Update: February 2002											
Marschner (3u)	104	EC-60	63	(25)	<0.01	19.3	NS	0	6	NS	NR
	93	EC-120	47	(7)		18.8		0	10		NR
Brufman (4u)	212	Epi-50	36	(3)	0.007	17	NS	1	7	26	31
	241	Epi-100	49	(5)		18		2	9	30	86
Riccardi (5u)	38	Epi-60	50		NS	23.1	NS	NR	NR	NR	NR
	36	Epi-120	51			24.7		NR	NR	NR	NR

* See appendix 1 for complete information on regimen, dosages and schedules, ** PR= partial response; CR = complete response

Table 1u. Randomized trials summarized in this practice guideline report.

Author, Year, (Reference number)	Treatment Groups
Epirubicin vs. Doxorubicin at Equal Doses*	
French, 1988 (1)	FAC-50 FEC-50
Italian, 1988 (2)	FAC-50 FEC-50
Lopez, 1989 (3)	FAC-50 FEC-50
Heidemann, 1990 (4)	AC–40 EC-40
Lawton, 1993 (5)	Doxorubicin-70 Epirubicin-70
Gasparini, 1990 (6)	Doxorubicin-20 Epirubicin-20
Castiglione, 1990 (7)	Doxorubicin-20 Epirubicin-20
Higher Dose Epirubicin vs. Doxorubicin*	
Perez, 1991 (8)	Doxorubicin-60 Epirubicin-90
Jain, 1985 (9)	Doxorubicin-60 Epirubicin-85
Humblet, 1988 (10)	VAC-50 VEC-65
EORTC, 1998 (1u)	Doxorubicin-75 Epirubicin-90
Gundersen, 1990 (2u)	Doxorubicin-20 Epirubicin-50
Escalating Doses of Epirubicin*	
Focan, 1993 (11)	FEC-50 FEC-100
Habeshaw, 1991 (12)	Epirubicin-50 Epirubicin-100
Bastholt, 1996 (13)	Epirubicin-40 Epirubicin-60 Epirubicin-90 Epirubicin-135
Marschner, 1994 (3u)	EC-60 EC-120
Brufman, 1997 (4u)	FEC-50 FEC-100
Riccardi, 2000 (5u)	FEC-60 FEC-120

* see Appendix I for full dose and administration information

Randomized Trials of Equal Doses of Epirubicin and Doxorubicin

Seven studies, six published reports (1-6) and one abstract (7), compared equal doses of epirubicin and doxorubicin. No difference in response rate or survival was observed for any of the studies. The results of the meta-analysis of response rate (partial plus complete response)

and complete response rate, for the six trials reporting numbers of patients with these outcomes and for the five trials reporting survival at one year, are given in Table 2. There was no difference between epirubicin and doxorubicin given at equal doses for response rate [RR, 1.04; 95% CI, 0.92 to 1.18; p=0.51], complete response rate [RR, 1.05; 95% CI, 0.74 to 1.49; p=0.77] or deaths at one year [RR, 1.01; 95% CI, 0.85 to 1.21; p=0.87]. Fewer patients receiving epirubicin had congestive heart failure [RR, 0.38; 95% CI, 0.14 to 1.04; p=0.059]; or other cardiotoxicity (ECG changes, decrease in ventricular ejection fraction, increase in pre-ejection period/left ventricular pre-ejection period ratio) [RR, 0.43; 95% CI, 0.24 to 0.77; p=0.0044] compared with patients receiving doxorubicin. Less neutropenia, nausea and vomiting, and alopecia was observed among patients receiving epirubicin. A pooled analysis of results from the four studies (2,3,5,6) reporting the number of patients with World Health Organization (WHO) grade 3 and 4 nausea and vomiting demonstrated a significant benefit for epirubicin [RR, 0.76; 95% CI, 0.63 to 0.92; p=0.0048]. Similar results were obtained from analysis of three studies (2,3,6) reporting the number of patients with Grade 3 and 4 neutropenia [RR, 0.52; 95% CI, 0.35 to 0.78; p=0.0017].

Table 2. Results of meta-analysis of randomized controlled trials comparing epirubicin and doxorubicin at equal doses (fixed effects model).

Outcome	# Trials	# Patients	Risk Ratio*	95% CI		P Value
				Low	High	
Response (partial + complete)	6	983	1.04	0.92	1.18	0.51
Complete response	6	983	1.05	0.74	1.49	0.77
1-year mortality	5	866	1.01	0.85	1.21	0.87
Congestive Heart Failure	6	983	0.38	0.14	1.04	0.059
Other cardiac toxicity	6	983	0.43	0.24	0.77	0.0044
Grade 3&4 nausea and vomiting	4	689	0.76	0.63	0.92	0.0048
Grade 3&4 neutropenia	3	634	0.52	0.35	0.78	0.0017

* Estimates >1.0 favour doxorubicin and estimates <1.0 favour epirubicin for both response and toxicity variables.

Update

Fossati et al conducted a systematic review of published randomized controlled trials of systemic treatments for metastatic breast cancer (6u). After pooling hazard ratios from published reports of six trials of epirubicin versus doxorubicin, Fossati reported an absolute survival benefit of 4% at one year in favour of doxorubicin-based chemotherapy compared with epirubicin-based chemotherapy. The pooled results reported in our practice guideline indicate that doxorubicin and epirubicin are equally efficacious at equal doses. Differences in the trials included in each meta-analysis may account for the difference in results and conclusions.

Meta-analysis - Survival

A comparison between the mortality data pooled for the PGI guideline report (7u) and for the analysis by Fossati appears in Table 2u. Hazard ratios for individual studies were not reported in the published meta-analysis but were presented graphically. For mortality, risk ratio and

hazard ratio results (including 95% confidence Interval [CI]) less than 1.0 favour epirubicin and results greater than 1.0 favour doxorubicin.

Table 2u: Mortality data in two meta-analyses of randomized trials of epirubicin versus doxorubicin in metastatic breast cancer*.

Study	CCOPGI practice guideline (7u) 1-year mortality risk ratio (95% CI)	Fossati et al (6u) Mortality hazard ratio (95% CI)
French, 1988 (1)	1.28 (0.84, 1.94)	> 1.0 significant difference
Italian, 1988 (2)	1.00 (0.75, 1.31)	1.0
Lopez, 1989 (3)	1.17 (0.71, 1.88)	> 1.0 (95% CI includes 1.0)
Lawton, 1993 (5)	0.63 (0.43, 0.91)	Not included
Gasparini, 1990 (6)	1.05 (0.57, 1.94)	1.0
Perez, 1991 (8)	Excluded from analysis	> 1.0 (95% CI includes 1.0)
Gundersen, 1990 (2u)	Excluded from analysis	> 1.0 (95% CI includes 1.0)
Total	1.01 (0.85, 1.21) p=0.87	1.13 (1.00, 1.27) p=0.05455

* risk ratio or hazard ratio >1.0 favours doxorubicin

Although the Lawton study (5) met all the eligibility criteria for the meta-analysis by Fossati et al, it was missed by their literature search and not included in the overview (6u). In five studies (1-3,5,6), epirubicin and doxorubicin were given at equal doses: 50 mg/m^2 every three weeks in three studies (1-3), 70 mg/m^2 every three weeks in the study by Lawton et al (5), and 20 mg/m^2 once a week in the study by Gasparini et al (6). Perez et al compared doxorubicin at a dose of 60 mg/m^2 with 90 mg/m^2 of epirubicin; both were given every three weeks (8). Gundersen et al (2u) gave 20/m^2 mg of doxorubicin weekly as a bolus injection to one group and 50 mg/m^2 of epirubicin every two weeks as a three-hour infusion to the other. In our practice guideline report, results from the studies of unequal doses (8,2u) were not pooled with those results from the studies of equal doses but were addressed elsewhere in the document.

Meta-analysis - Tumour response

Both our practice guideline and Fossati's meta-analysis failed to detect a significant difference in tumour response rate between epirubicin and doxorubicin.

Meta-analysis – Adverse effects

Both Fossati et al and the PGI reported pooled results for cardiac toxicity and neutropenia. These are summarized in Table 3u. Both the risk ratios and the odds ratios for neutropenia and cardiac toxicity can be interpreted in a similar manner (i.e., a ratio of less than 1.0 indicates that patients on epirubicin are less likely to experience neutropenia or adverse cardiac effects than those on doxorubicin).

Table 3u: Toxicity data included in two meta-analyses of randomized trials of epirubicin versus doxorubicin in metastatic breast cancer*.

Outcome	PGI practice guideline (7u) Pooled risk ratio (95% CI	Fossati et al (6u) Pooled odds ratio (95% CI)
Neutropenia	0.52 (0.35, 0.78)	0.55 (CI < 1.0)
Cardiac toxicity	CHF: 0.38 (0.14, 1.04) other: 0.43 (0.24, 0.77)	all cardiac toxicity: 0.52 (CI < 1.0)

* risk ratio or odds ratio <1.0 favours epirubicin, CHF = congestive heart failure

Randomized Trials of Epirubicin at Higher Doses than Doxorubicin

Data comparing epirubicin at higher doses than doxorubicin from the two new randomized trials, along with data from the three randomized trials reported in the original practice guideline report, are summarized in Table 1b.

Three studies, two published reports (8,9) and one abstract (10), compared a higher dose of epirubicin with a lower dose of doxorubicin. No difference in response rate or survival was observed for any of the studies. Congestive heart failure occurred in slightly fewer patients receiving epirubicin, and those patients also had less other cardiotoxicity. One study reported less nausea and vomiting, and two studies reported no difference in other side effects.

Update

The European Organization for Research and Treatment of Cancer Breast Cancer Cooperative Group (EORTC) randomized 259 women with metastatic breast cancer to receive either 75 mg/m^2 of doxorubicin or 90 mg/m^2 of epirubicin every 3 weeks (1u). Almost all participants had received one prior chemotherapy regimen for metastatic disease. Response and survival data were available for 232 patients, and 229 patients were evaluable for adverse effects.

There were no significant differences in response rates among patients who received doxorubicin compared with those who received epirubicin (36% vs. 28%, p=0.173), or in overall survival (11.8 months vs. 11.0 months, p=0.196), or in grade 3 and 4 nausea and vomiting (32% vs. 27%, p=0.304). Three patients in the doxorubicin group and four in the epirubicin group experienced a grade 3 or 4 infection. There were three deaths associated with infectious complications in the doxorubicin group and none in the epirubicin group.

Gundersen et al (2u) randomized 168 patients to receive 20 mg/m^2 of doxorubicin as a weekly bolus injection or 50 mg/m^2 of epirubicin every 2 weeks as a 3-hour infusion. One hundred and forty-nine patients were evaluable for response, and 160 patients were evaluable for toxicity. None of the patients had prior chemotherapy for metastatic disease. Patients in the doxorubicin arm had higher response rates than those in the bi-weekly epirubicin arm (36% vs. 22%, p=0.10) but the difference was not statistically significant. There were no significant differences in survival or in response duration between the two groups; however, patients in the epirubicin arm had significantly higher rates of nausea (28% vs. 2%, p=0.0002), vomiting (27% vs. 4%, p=0.001), and alopecia (24% vs. 11%, p= 0.05).

Randomized Trials of Escalating Doses of Epirubicin

Data comparing escalating doses of epirubicin from the three new randomized trials, as well as data from the three randomized trials reported in the original practice guideline report, are summarized in Table 1c.

Three studies, all published reports (11-13), evaluated escalating doses of epirubicin. These studies showed increased response rates with higher doses of epirubicin, but there was

no difference in overall survival. Two studies (12,13) reported more nausea and vomiting associated with the higher doses of epirubicin. Other toxicities associated with the higher doses of epirubicin were more alopecia, myelosuppression, and mucositis (12), increased anemia and granulocytopenia (11), more stomatitis, and decreased white blood counts and platelets (13).

Update

Marschner et al (3u) randomized 270 patients with no prior chemotherapy to 60 mg/m^2 of epirubicin or 120 mg/m^2 of epirubicin, administered with 600 mg/m^2 of cyclophosphamide every 3 weeks. Results are based on 197 evaluable patients. The higher dose group had significantly higher response rates (63% vs. 47%, p<0.01) but similar time to progression (9.9 months vs. 9.57 months, p=NS) and no difference in overall survival (18.8 months vs. 19.3 months, p=NS). Patients in the higher dose group had more infections (p<.05), and there were 4 treatment related deaths, but there were no differences in cardiotoxicity and no cases of congestive heart failure.

Brufman et al (4u) randomized 456 women who had received no prior chemotherapy for metastatic breast cancer to either 50 mg/m^2 of epirubicin (FEC-50 group) or to 100 mg/m^2 of epirubicin (FEC-100 group) in combination with 5-fluorouracil and cyclophosphamide. Efficacy results were available for 453 patients, and 447 patients were evaluable for adverse effects.

Patients in the FEC-100 group experienced higher response rates than patients in the FEC-50 group (49% vs. 36%, p=0.007) but with greater grade 3 and 4 neutropenia (86% vs. 31%, p < 0.001), mucositis (10% vs. 0.4%, p=0.015), and alopecia (72% vs. 56%, p<0.001) with no difference in overall survival (18 months vs. 17 months, p=0.54). Eight percent of the FEC-100 group experienced grade 4 infections or febrile neutropenia compared with 0.4% of the FEC-50 group. There were two septic deaths in each group and one death in the FEC-100 group due to a cerebrovascular accident in the absence of thrombocytopenia. An attempt to measure quality of life failed because of poor compliance with questionnaire completion.

In the study by Riccardi et al (5u), 74 women with metastatic breast cancer were randomized to receive one of two doses of epirubicin: 60 mg/m^2 (FEC-60 group) or 120 mg/m^2 (FEC-120 group) in combination with 5-fluorouracil and cyclophosphamide. This study was prematurely closed to recruitment based on the results of the following interim analysis. Results are available for 73 of the 74 randomized patients. Patients in the FEC-120 group had a significantly longer time to progression than patients in the FEC-60 group (19.2 vs. 13.1 months, p= 0.04), but there were no significant differences in overall survival (33% vs. 24%, p = NS), median survival (24.7 months vs. 23.1 months, p= NS), or response rate (51% vs. 50%, p=NS). Compared to patients in the FEC-60 group, patients in the FEC-120 group experienced less leucopenia (p=NS) but significantly more grade III-IV thrombocytopenia (p<0.0001) and anemia (p<0.005).

Quality-of-life data were available for 66% of patients three months after ending treatment. Quality of life was measured using the EORTC quality-of-life questionnaire (EORTC QLQ-C30 [version 2.0] and QLQ-BR23) and the Spitzers QL-index. There were no significant differences between the two treatment arms in any of the quality-of-life measures.

V. INTERPRETIVE SUMMARY

Randomized controlled trials in advanced breast cancer have shown that epirubicin and doxorubicin have equivalent efficacy when measured by response rates or survival. In our pooled analysis of six trials comparing equal doses of these drugs, alone or as part of combination therapy, response rates were equivalent. In doses equal to doxorubicin, epirubicin had less toxicity, when measured by conventional toxicity scores, and fewer episodes of congestive heart failure. No studies have reported data on quality of life.

Epirubicin can be given in higher cumulative doses and for longer periods before causing cardiotoxicity, but this approach has not been shown to improve survival or tumour response. Epirubicin can also be given in higher doses per course, but this lessens the advantage in reduced toxicity. Some evidence exists that higher doses of epirubicin improve response rate compared with lower doses (11-13), but higher doses of epirubicin have not been shown to be better than standard doses of doxorubicin.

The limited data available in neoadjuvant treatment of locally advanced breast cancer do not show a difference in response between doxorubicin and epirubicin (14). No survival data are available.

Update

In the comparison of doxorubicin and epirubicin at equal doses, the Fossati meta-analysis is of interest in that it reported a hazard ratio for mortality suggesting an almost significant benefit in favour of doxorubicin. However, our direct contact with Fossati regarding his exclusion of the Lawton study, which tends to influence our meta-analysis to a more neutral position, indicated that Fossati would have included this study if he had known of its existence. In fact, both meta-analyses suggest no significant difference between epirubicin and doxorubicin used at equal doses.

Two new studies comparing doxorubicin with epirubicin given at higher doses brought the number of randomized trials to five in total. These studies show no differences in tumour response rate or in survival. The EORTC study favours a trend toward less cardiac toxicity with epirubicin, while the trial by Gundersen reports greater toxicity with a bi-weekly epirubicin regimen as compared to a weekly doxorubicin regimen.

In comparing escalating doses of epirubicin, three new trials brought the total number of randomized trials to six. Higher doses of epirubicin were more efficacious but were also more likely to cause greater grade 3 and 4 neutropenia, with no difference in overall survival. There were no significant differences in cardiac events between the higher and lower doses.

In summary, the new evidence continues to support the interpretation that epirubicin and doxorubicin have similar efficacy when given in equal doses, as well as when epirubicin is given in somewhat higher doses than doxorubicin. There is a trend, however, toward fewer adverse effects in epirubicin-treated patients (i.e., CHF). Higher doses of epirubicin appear more efficacious than lower doses, at least in terms of response rate, but also are more likely to cause grade 3 and 4 neutropenia.

We believe that the new evidence is consistent with our previous conclusion that epirubicin, at doses equivalent to or at doses somewhat higher than those of doxorubicin, is equally efficacious and less toxic than doxorubicin. Epirubicin taken to much higher doses may be more efficacious but is also more toxic.

VI. ONGOING TRIALS

The Breast Cancer DSG is not aware of any ongoing randomized trials of epirubicin versus doxorubicin for metastatic breast cancer.

VII. DISEASE SITE GROUP CONSENSUS PROCESS

The draft evidence-based recommendation, which was written by a member of the Systemic Treatment DSG, was reviewed and discussed by the Breast Cancer DSG. Evidence from randomized trials suggests that epirubicin and doxorubicin, when delivered at equivalent doses, are equally efficacious. However, epirubicin is slightly less toxic than doxorubicin. There is no evidence that, at equal doses, epirubicin is superior to doxorubicin in improving either response rates or overall survival. Given that doxorubicin has been a mainstay of chemotherapy treatment for metastatic breast cancer for many years, the Breast DSG felt

that the evidence of efficacy was not strong enough to recommend a definitive switch from the use of doxorubicin to the use of epirubicin. However, given that the two agents appear to be equally efficacious and given that epirubicin has a lower incidence of cardiac toxicity and is generally less toxic than doxorubicin, the Breast Cancer DSG does support the use of epirubicin as a reasonable alternative to doxorubicin.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

This section describes the external review activities undertaken for the original guideline report.

Draft Practice Guideline

Target Population

These recommendations apply to adult patients with metastatic breast cancer for whom the goal of treatment is palliation.

Draft Recommendations

For the treatment of metastatic breast cancer in which the goal of treatment is palliation, epirubicin (at doses equivalent to doxorubicin) has been shown to be equally efficacious and somewhat less toxic than doxorubicin. Doxorubicin, however, is an acceptable alternative.

Practitioner Feedback

Based on the evidence contained in the original guideline report and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

In 1996, practitioner feedback was obtained through a mailed survey of 91 practitioners in Ontario. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey were reviewed by the Breast Cancer DSG.

Results

Seventy percent of the surveys were returned. Ninety-eight percent agreed or strongly agreed with the methods and data synthesis, 94% endorsed the evidence-based report, and 76% endorsed the evidence-based report as a practice guideline.

In their written comments, the respondents requested a cost-benefit analysis comparing epirubicin with doxorubicin.

Modifications/Actions

The Breast Cancer DSG felt that the points raised regarding economic evaluation were related to the formulation of policy rather than an evidence-based recommendation. The draft recommendation was approved, without changes, as a practice guideline by the Breast Cancer DSG and the PGCC.

IX. PRACTICE GUIDELINE

This practice guideline is unchanged from the original recommendations approved in 1997.

Target Population
These recommendations apply to adult patients with metastatic breast cancer for whom the goal of treatment is palliation.

Recommendations
Epirubicin, at doses equivalent to doxorubicin, has been shown to be equally efficacious and less toxic than doxorubicin. Doxorubicin, however, is an acceptable alternative.

X. JOURNAL REFERENCE

Findlay BP, Walker-Dilks C, the Provincial Breast Cancer Disease Site Group and the Provincial Systemic Treatment Disease Site Group. Epirubicin, alone or in combination chemotherapy, for metastatic breast cancer. *Canc Prev Control*, 1998;2(3):140-146.

XI. ACKNOWLEDGEMENTS

The Systemic Treatment Disease Site Group and the Breast Disease Site Group would like to thank Dr. B. Findlay and Ms. C. Walker-Dilks for taking the lead in drafting and revising this practice guideline.

The Breast Cancer Disease Site Group would like to thank Dr. Kathy Pritchard for taking the lead in updating this practice guideline report.

For a full list of members of the Breast Cancer Disease Site Group, please visit the CCO Web pages at http://www.cancercare.on.ca/.

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Update

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Appendix 1. Dosages and schedules for studies summarized in Tables 1a, 1b and 1c.

French (1): Doxorubicin or epirubicin, 50 mg/m^2; 5-FU, 500 mg/m^2; and cyclophosphamide, 500 mg/m^2 administered day 1 every 3 weeks.

Italian (2) and Lopez (3): Doxorubicin or epirubicin, 50 mg/m^2; 5-FU, 500 mg/m^2; and cyclophosphamide, 500 mg/m^2 administered day 1 every 3 weeks. 5-FU administered day 1 and 8.

Heideman (4): Doxorubicin or epirubicin, 40 mg/m^2; and cyclophosphamide, 600 mg/m^2 administered every 3 weeks.

Lawton (5): Doxorubicin or epirubicin, 70 mg/m^2 administered every 3 weeks.

Gasparini (6) and Castiglione (7): Doxorubicin or epirubicin, 20 mg/m^2 per week.

Perez (8): Doxorubicin, 60 mg/m^2 or epirubicin, 90 mg/m^2 administered every 3 weeks.

Jain (9): Doxorubicin, 60 mg/m^2 or epirubicin, 85 mg/m^2 administered every 3 weeks.

Humblet (10): Doxorubicin, 50 mg/m^2 or epirubicin 65 mg/m^2; cyclophosphamide, 500 mg/m^2; and vindesine, 2 mg/m^2 administered every 3 weeks.

Focan (11): Epirubicin, 50 mg/m^2 day 1 and 8 or epirubicin, 50 mg/m^2 day 1; 5-FU, 500 mg/m^2; and cyclophosphamide, 500 mg/m^2 every 3 weeks.

Habeshaw (12): Epirubicin 50 mg/m^2 (16 courses) or epirubicin, 100 mg/m^2 (8 courses); and oral prednisolone, 25 mg 2 times/d for 5 days.

Bastholdt (13): Epirubicin, 40, 60, 90, or 135 mg/m^2 every 3 weeks.

Update
EORTC (1u): Doxorubicin vs. Epirubicin - 75 mg/m^2 of doxorubicin or 90 mg/m^2 of epirubicin administered every three weeks.

Gundersen (2u): Doxorubicin vs. Epirubicin - 20 mg/m^2 of weekly doxorubicin or 50 mg/m^2 of biweekly epirubicin.

Marschner (3u) EC vs. EC - 60 mg/m^2 of epirubicin or 120 mg/m^2 of epirubicin, administered with 600 mg/m^2 of cyclophosphamide every 3 weeks.

Brufman (4u): FEC vs. FEC - 50 mg/m^2 of epirubicin or 100 mg/m^2 of epirubicin administered with 500 mg/m^2 of 5-FU and 500 mg/m^2 of cyclophosphamide every 3 weeks.

Riccardi (5u) FEC vs. FEC - 60 mg/m^2 of epirubicin or 120 mg/m^2 of epirubicin, supported with G-CSF, administered with 600 mg/m^2 of 5-FU and 600 mg/m^2 of cyclophosphamide on day 1 every 3 weeks.

Document Assessment and Review Tool.

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DOCUMENT ASSESSMENT AND REVIEW TOOL

Number and title of document under review	UPG #1-6 Epirubicin, as a Single Agent or in Combination, for Metastatic Breast Cancer
Date of current version	April 30, 2003
Clinical reviewer	Dr. Maureen Trudeau Dr. Andrea Eisen
Research coordinator	Rovena Tey
Date initiated	June 2010
Date and final results / outcomes	**June 11, 2010 (ARCHIVED)**
Instructions. Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.	
1. Is there still a need for a guideline covering one or more of the topics in this document **as is**? Answer Yes or No, and explain if necessary:	1. NO • Guideline 1-6 should be **ARCHIVED**. If No, then the document should be **ARCHIVED**[1] with no further action; **go to 11**. If Yes, then **go to 2**.
2. Are all the current recommendations based on the current questions **definitive**[*] or **sufficient**[§], and have less than **5 years elapsed** since the latest search? Answer Yes or No, and explain if necessary:	2. If Yes, the document can be **ENDORSED**[2] with no further action; **go to 11**. If No, **go to 3**.
3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, providing references of known evidence:	3. If Yes, the document should be taken off the Web site as soon as possible. A **WARNING**[¶] should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons. If No, g**o to 4**.
4. Do current resources allow for an updated literature search to be conducted at this time? Answer Yes or No, and explain as necessary. Provide an expected date of completion of the updated search, if applicable:	4. If No, a **DEFERRAL**[3] should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis. If Yes, go **to 5**.
5a. **Guideline Research Questions.** Please review the original guideline research questions below and if applicable, list any MINOR changes to the questions that now must be considered. If a question is no longer relevant, it can be deleted. The Document Assessment & Review process evaluates the guideline **as is** and CANNOT accommodate significant changes to the questions or the addition of new questions introducing new patient populations or new agents/interventions because if this what is required in order to make this guideline relevant, then a brand new document should be produced and this guideline as is should be ARCHIVED (i.e., go back to Q1 of this form and answer NO).	

5b. **Inclusion and Exclusion criteria.** List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence).	
5c. Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below.	
Go to 6.	
6. Is the volume and content of the new evidence so extensive such that a simple update will be difficult?	6. If Yes, then the document should be **ARCHIVED** with no further action; **go to 11**. If No, **go to 7**.
7. On initial review, does the newly identified evidence support the **existing recommendations**? Do the current recommendations **cover all relevant subjects** addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary:	7. If Yes, the document can be **ENDORSED**. If No, **go to 8**.
8. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:	8. If Yes, a **WARNING** note will be placed on the web site. If No, **go to 9**.
9. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	9. If Yes, the document update will be **DEFERRED**, indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, **go to 10.**
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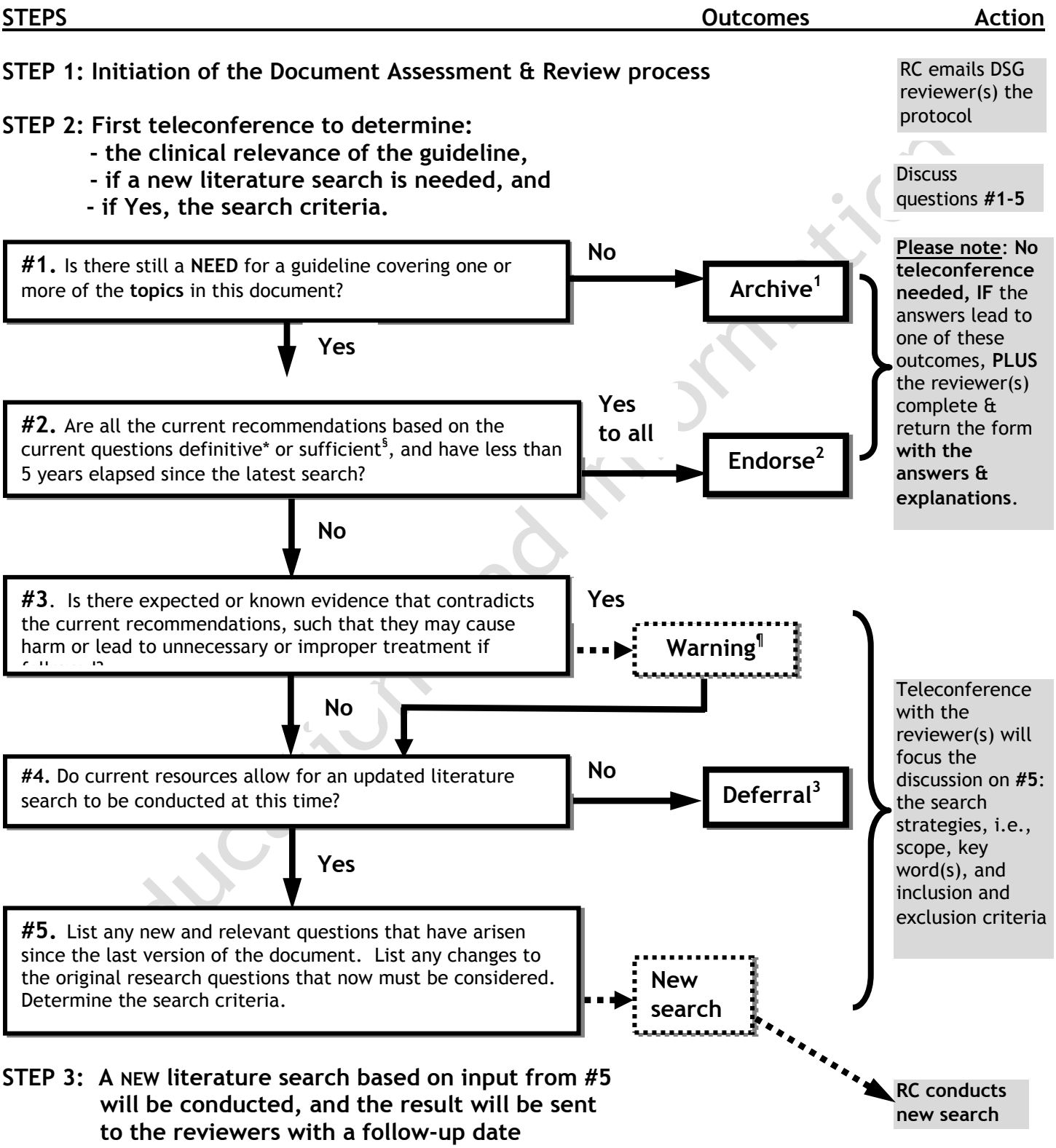
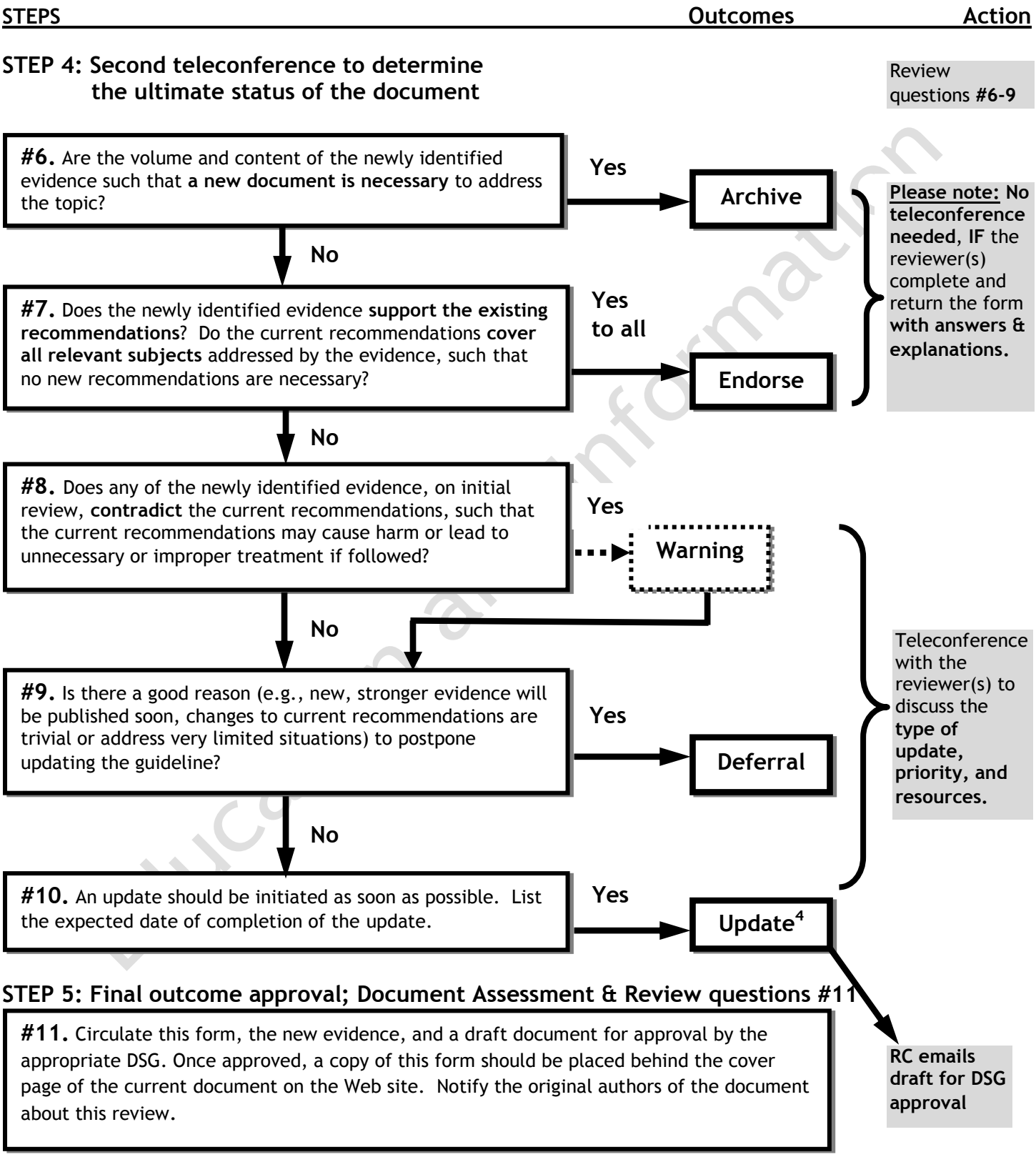
11. Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the Web site. Notify the original authors of the document about this review.	
DSG Approval Date:	**June 11, 2010**

DOCUMENT ASSESSMENT & REVIEW 5-STEP FLOW CHART



FLOW CHART (cont.)



DOCUMENT ASSESSMENT AND REVIEW DEFINITIONS

Document Assessment and Review Terms

***DEFINITIVE RECOMMENDATIONS** – Definitive means that the current recommendations address the relevant subject area so fully that it would be very surprising to identify any contradictory or clarifying evidence.

§ SUFFICIENT RECOMMENDATIONS – Sufficient means that the current recommendations are based on consensus, opinion and/or limited evidence, and the likelihood of finding any further evidence of any variety is very small (e.g., in rare or poorly studied disease).

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Document Assessment and Review Outcomes

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2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

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4. **UPDATE –** An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.