ON-LINE APPENDIX

Search Strategies

PubMed

((“Brain Neoplasms”[MeSH Terms] OR “Glioma”[MeSH Terms] OR glioma* OR (glioblastoma* OR “glioblastoma multiforme”) OR (astrocytoma* OR “anaplastic astrocytoma”) OR (oligodendrocytoma* OR “anaplastic oligodendrocytoma”) OR (brain AND (tumor* OR tumour*)) OR (neuroectodermal AND (tumor* OR tumour*)) OR ependymoma* OR oligodendroglioma*)) AND (“Tomography, Emission-Computed”[MeSH Terms] OR (positron AND emission AND tomograph*) OR pet) AND “humans”[MeSH Terms]

Scopus

(TITLE-ABS-KEY (glioma*) OR TITLE-ABS-KEY (glioblastoma*) OR TITLE-ABS-KEY (glioblastoma PRE/0 multiforme) OR TITLE-ABS-KEY (astrocytoma*) OR TITLE-ABS-KEY (anaplastic PRE/0 astrocytoma) OR TITLE-ABS-KEY (oligodendrocytoma*) OR TITLE-ABS-KEY (anaplastic PRE/0 oligodendrocytoma) OR TITLE-ABS-KEY (brain tumo*r*) OR TITLE-ABS-KEY (neuroectodermal PRE/0 tumo*r*) OR TITLE-ABS-KEY (ependymoma*) OR TITLE-ABS-KEY (oligodendroglioma*) AND TITLE-ABS-KEY (positron PRE/0 emission PRE/0 tomograph*) OR TITLE-ABS-KEY (pet).

PUBLICATIONS EXCLUDED AFTER FULL-TEXT SCREENING

Relevant but <10 Patients (n = 7)

1. Lichy MP, Bachert P, Henze M, et al. **Monitoring individual response to brain-tumor chemotherapy: proton MR spectroscopy in a patient with recurrent glioma after stereotactic radiation therapy**. *Neuroradiology* 2004;46:126–29
2. Pruim J, Willemsen AT, Molenaar WM et al. **Brain tumors: L-[1-C-11]tyrosine PET for visualization and quantification of protein synthesis rate**. *Radiology* 1995;197:221–26
3. Kim EE, Chung SK, Haynie TP et al. **Differentiation of residual or recurrent tumors from posttreatment changes with F-18 FDG PET.** *Radiographics* 1992;12:269–79
4. Di Chiro G, Oldfield E, Wright DC, et al. **Cerebral necrosis after radiation therapy and/or intra-arterial chemotherapy for brain tumor: PET and neuropathologic studies.** *AJR Am J Roentgenol* 1988;150:189–97
5. Glantz MJ, Hoffman JM, Coleman RE et al. **Identification of early recurrence of primary central nervous system tumors by [18F]fluorodeoxyglucose positron emission tomography.** *Ann Neurol* 1991; 29:347–55
6. Ogawa T, Kanno I, Shishido F et al. **Clinical value of PET with 18F-fluorodeoxyglucose and L-methyl-11C-methionine for diagnosis of recurrent brain tumor and radiation injury.** *Acta Radiol* 1991;32: 197–202
7. Chao ST, Suh JH, Raja S, et al. **The sensitivity and specificity of FDG PET in distinguishing recurrent brain tumor from radionecrosis in patients treated with stereotactic radiosurgery.** *Int J Cancer* 2001;96: 191–97

Partially Eligible but Pertinent Data Not Extractable (n = 6)

8. Yamane T, Sakamoto S, Senda M. **Clinical impact of (11)C-methionine PET on expected management of patients with brain neoplasm.** *Eur J Nucl Med Mol Imaging* 2010;37:685–90
9. Chen W, Silverman DH, Delaloye S, et al. **18F-FDOPA PET imaging of brain tumors: comparison study with 18F-FDG PET and evaluation of diagnostic accuracy.** *J Nucl Med* 2006;47:904–11
10. Henze M, Mohammed A, Schlemmer HP et al. **PET and SPECT for detection of tumor progression in irradiated low-grade astrocytoma: a receiver-operating-characteristic analysis.** *J Nucl Med* 2004;45:579–86
11. Wang SX, Boethius J, Ericson K. **FDG-PET on irradiated brain tumor: ten years’ summary.** *Acta Radiol* 2006;47:85–90
12. Deshmukh A, Scott JA, Palmer EL, et al. **Impact of fluorodeoxyglucose positron emission tomography on the clinical management of patients with glioma.** *Clin Nucl Med* 1996;21:720–25
13. Maldonado A, Alfonso JM, Ossola G, et al. **The role of PET-FDG in resolving diagnostic doubt: recurrence versus radionecrosis in brain tumors: experience in 94 patients.** *Riv Neuroradiol* 2003;16:887–90

All Recurrent Cases (n = 4)

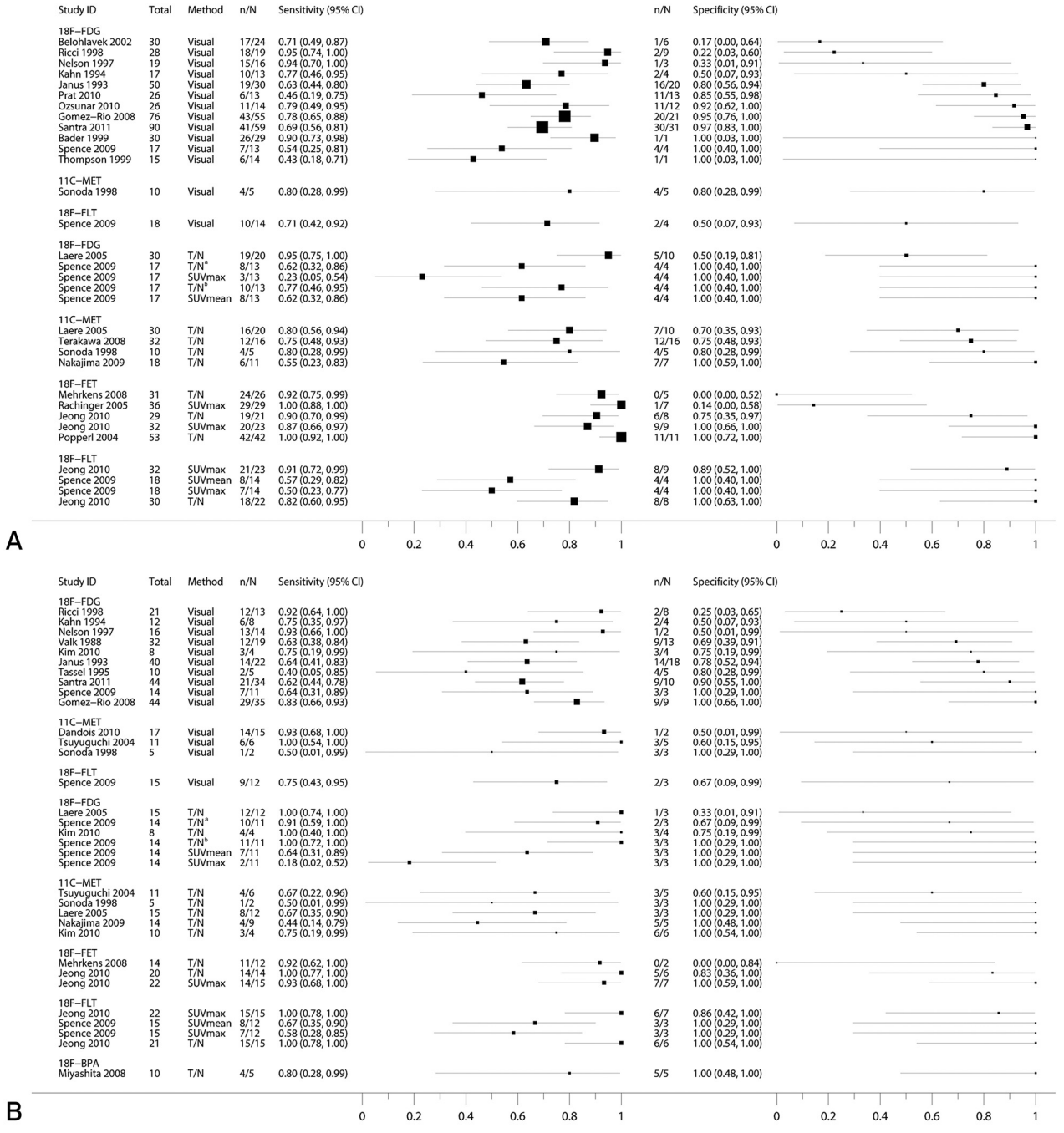
14. Hübner KF, Thie JA, Smith GT, et al. **Positron emission tomography (PET) with 1-aminocyclobutane-1-[(11)C]carboxylic acid (1-[(11)C]-ACBC) for detecting recurrent brain tumors.** *Clin Positron Imaging* 1998;1:165–73
15. Ishikawa M, Kikuchi H, Miyatake S, et al. **Glucose consumption in recurrent gliomas.** *Neurosurgery* 1993;33:28–33
16. Yamamoto Y, Wong TZ, Turkington TG, et al. **3′-deoxy-3′-[F-18]fluorothymidine positron emission tomography in patients with recurrent glioblastoma multiforme: comparison with Gd-DTPA enhanced MR imaging.** *Mol Imaging Biol* 2006;8:340–47
17. Grosu AL, Astner ST, Riedel E, et al. **An interindividual comparison of O-(2- [(18)F]fluoroethyl)-L-tyrosine (FET)- and L-[methyl-(11)C]methionine (MET)-PET in patients with brain gliomas and metastases.** *Int J Radiat Oncol Biol Phys* 2011;81:1049–58

Irrelevant (n = 5)

18. Weber WA, Wester HJ, Grosu AL et al. **O-(2-[18F]fluoroethyl)-L-tyrosine and L-[methyl-11C]methionine uptake in brain tumors: initial results of a comparative study.** *Eur J Nucl Med* 2000;27: 542–49
19. Blasberg RG, Roelcke U, Weinreich R et al. **Imaging brain tumor proliferative activity with [124I]iododeoxyuridine.** *Cancer Res* 2000;60:624–35
20. Willemsen AT, van WA, Paans AM et al. **In vivo protein synthesis rate determination in primary or recurrent brain tumors by using L-[1–11C]-tyrosine and PET.** *J Nucl Med* 1995;36:411–19
21. Pirotte B, Goldman S, David P et al. **Stereotactic brain biopsy guided by positron emission tomography (PET) with [F-18]fluorodeoxyglucose and [C-11]methionine.** *Acta Neurochir Suppl* 1997;68:133–38
22. Ledezma CJ, Chen W, Sai V, et al. **18F-FDOPA PET/MR imaging fusion in patients with primary/recurrent gliomas: initial experience.** *Eur J Radiol* 2009;71:242–48

Not a Dedicated PET Scanner (n = 1)

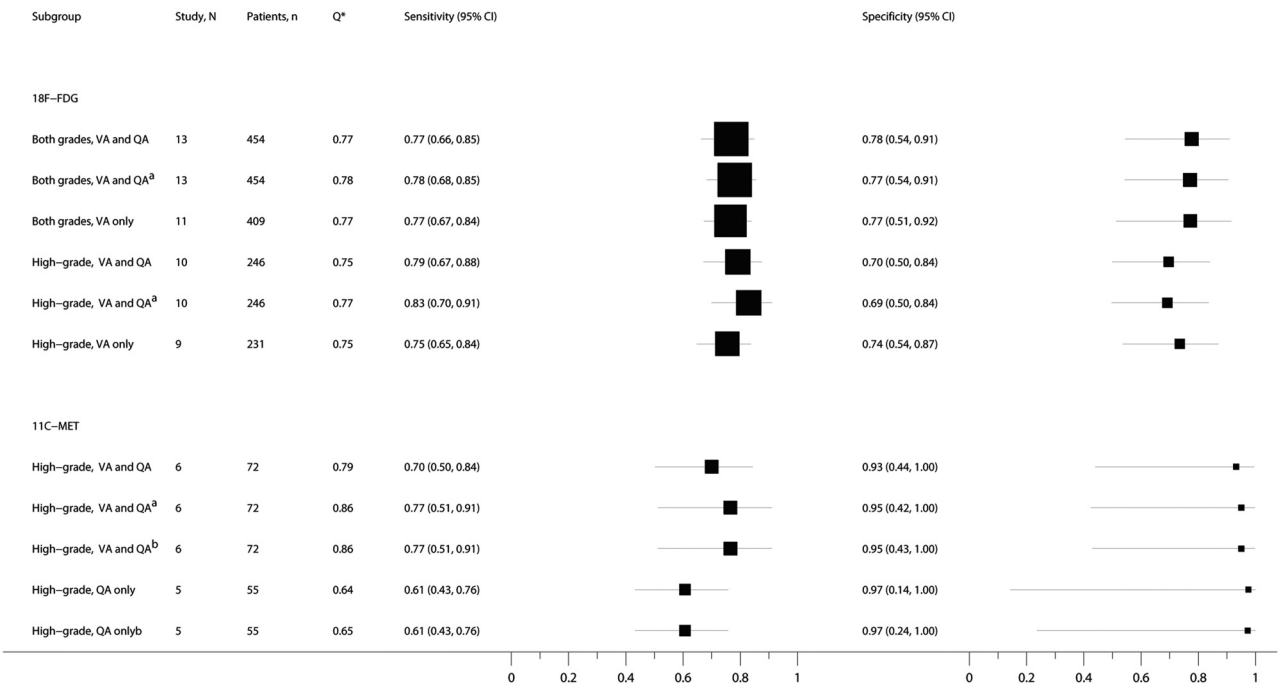
23. Stokkel M, Stevens H, Taphoorn M, et al. **Differentiation between recurrent brain tumor and postradiation necrosis: the value of 201Tl SPET versus 18F-FDG PET by using a dual-headed coincidence camera–a pilot study.** *Nucl Med Commun* 1999;20:411–17



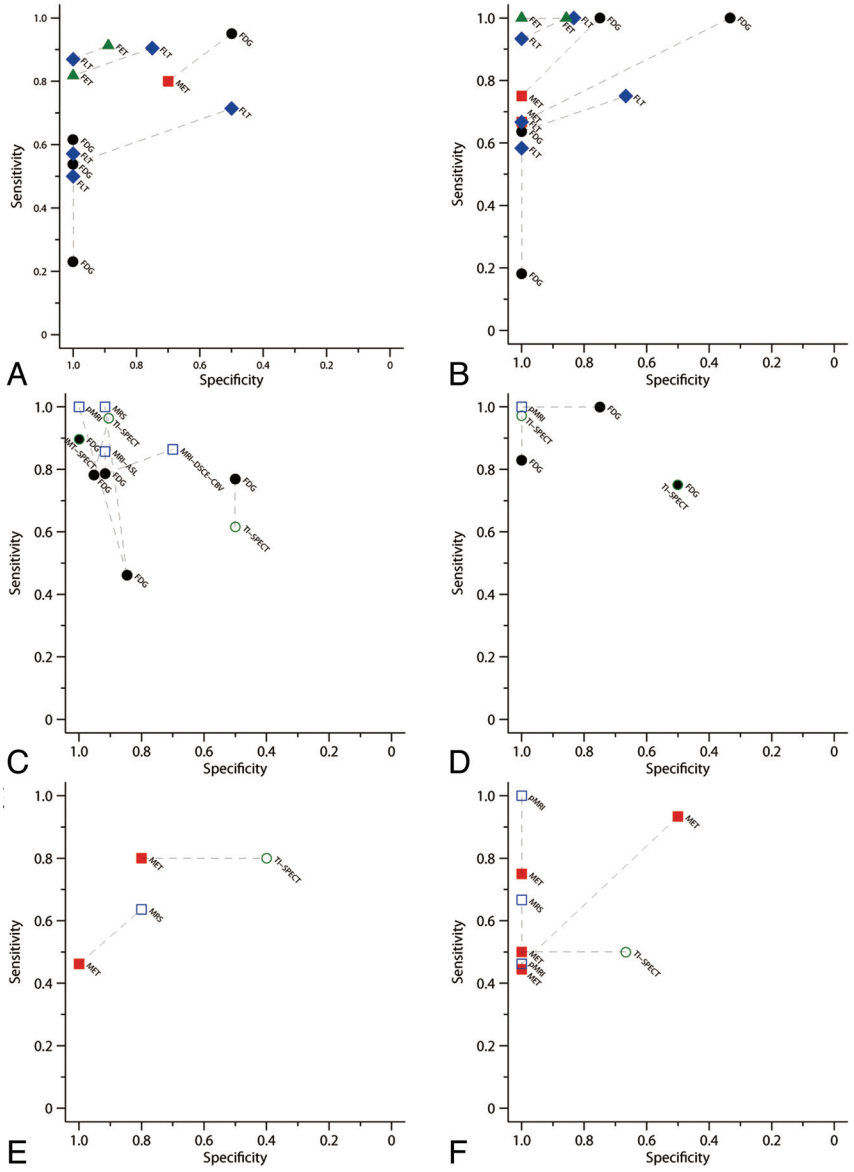
ON-LINE FIG 1. Sensitivity and specificity of PET for differentiating glioma recurrence from treatment-induced necrosis (for both low- and high-grade gliomas [*A*] and high-grade glioma only [*B*]). Squares (proportional to the number of patients) represent the point estimates of sensitivity and specificity; extending lines represent the 95% confidence interval (CI) of each estimate; and n/n denotes true-positive cases divided by recurrent cases for sensitivity, and true-negative cases divided by nonrecurrent cases for specificity. BPA indicates ^{18}F-boronophenylalanine; V, visual assessment.

[a] tumor-to-cortex ratio.

[b] tumor-to-white matter ratio.



ON-LINE FIG 2. Subgroup and sensitivity analyses of sensitivity and specificity. Squares (proportional to the number of patients) represent point estimates of sensitivity and specificity; extending lines represent the 95% confidence interval of each estimate. QA indicates, quantitative assessment; VA, visual assessment; Q*, "Q-star" statistic, a global summary of the ROC curve (see text for details).
[a] Sensitivity analyses preferring quantitative assessment for ^{18}F-FDG PET and visual assessment for ^{11}C-MET PET (see text for details).
[b] Sensitivity analyses preferring the optimal cutoff threshold for defining positive and negative scans by receiver operating characteristic analysis (see text for details).



ON-LINE FIG 3. Comparative accuracy of PET for differentiating recurrent glioma from treatment-induced necrosis. Comparisons among different PET tracers for both high- and low-grade glioma histology (*A*) and high-grade glioma only (*B*), between ^{18}F-FDG PET and other imaging modalities for any glioma histology (*C*) and high-grade glioma (*D*), and between ^{11}C-MET PET and other imaging modalities for both high- and low-grade glioma histology (*E*) and high-grade glioma only (*F*). Closed and open symbols, respectively, indicate PET and comparator imaging modalities. Dashed lines connect estimates for pairs of different PET tracers in (eg, ^{18}F-FDG-PET versus ^{11}C-MET) or of PET and a comparator imaging test (eg, ^{18}F-FDG-PET versus Tl-SPECT) compared in a study. Closed circle (black), square (red), triangle (green), and diamond (blue), respectively, indicate PET with FDG, MET, FET, and FLT. Open circle (green) and square (blue), respectively, indicate SPECT and MR imaging–based novel imaging.

ON-LINE TABLE 1: Study characteristics of positron-emission tomography to differentiate recurrence from treatment-related necrosis in treated glioma

Study	Country	Study Period (yr)	Patient (No.)	Institution (No.)	Design	Clinical Context	Indication	Tracer	Comparator Imaging Tests	Prior Imaging Tests	Median Time (from Dx/Tx) to Imaging (range) (mo)	Reference Standard	Median Follow-Up after PET (range) (mo)
Any grades													
Janus et al 1993[16]	US	ND	50	1	Retrospective	ND	Suspected recurrence, radiation necrosis, or others by MRI	FDG	None	Enhanced MRI	11 (1–208)	Bx or clinical follow-up	12 (5–27)[a]
Kahn et al 1994[17]	US	ND	17	1	Prospective	ND	Suspected recurrence by deteriorating clinical course or change in MRI or CT	FDG	Tl-SPECT	Enhanced MRI or CT	33 (6–120) (Dx)	Bx or clinical follow-up	12 (1–32)
Nelson et al 1997[18]	US	1994–1995	19	1	Retrospective	ND	Suspected recurrence by MRI	FDG	None	Enhanced MRI	ND	Clinical follow-up only	8 (2–22)
Ricci et al 1998[19]	US	1993–1995	31	1	Retrospective	ND	Suspected recurrence or radiation necrosis by symptoms and MRI	FDG	None	Enhanced MRI	ND	Bx only	NA
Sonoda et al 1998[20]	Japan	ND	10	1	Retrospective	ND	Highly suggestive of recurrence by MRI	MET	Tl-SPECT	MRI	ND	Bx/surgery or clinical follow-up for 3 mo	ND
Bader et al 1999[21]	Germany	ND	30	1	Prospective	ND	Suspected recurrence	FDG	IMT-SPECT	ND	24 (6–144) (Tx)	Bx only	NA
Thompson et al 1992[2]	US	ND	15	1	Retrospective	ND	Suspected progression or necrosis by CT or MRI	FDG	None	MRI or CT	37[b] (7–90) (Tx)	Bx only	NA
Belohlávek et al 2002[23]	Czech	ND	29	1	Retrospective	ND	Suspected recurrence	FDG	None	Enhanced MRI	ND (4–64) [Tx]	Bx or clinical follow-up	ND (12–28)
Pöpperl et al 2004[24]	Germany	ND	53	1	Retrospective	Post 1st- and 2nd-line	Suspected recurrence	FET	None	MRI or CT	36 (4–180) (Dx)	Bx or clinical follow-up for 2 mo by MRI	Mean 34 (16–69)[c]
Van Laere et al 2005[25]	Belgium	1997–2000	30	1	Retrospective	Post 1st-line	To differentiate tumor recurrence from radiation necrosis	FDG, MET	None	MRI or CT	48 (1–216)	Survival/death at last follow-up	15
Rachinger et al 2005[26]	Germany	2001–2003	36	1	Retrospective	ND	Suspected recurrence or progression	FET	None[d]	MRI	ND	Bx or clinical follow-up	9 (5–18)[e] 8 (4–20)[f]
Gómez-Río et al 2008[27]	Spain	2002–2005	76	1	Prospective	Post 1st-line	Suspected recurrence by clinical symptoms and MRI[g]	FDG	Tl-SPECT	MRI	ND	Bx or clinical follow-up[h]	31 (9–48)
Mehrkens et al 2008[28]	Germany	2003–2004	31	1	Prospective	ND	Suspected recurrence or progression by MRI	FET	None	Enhanced MRI	ND	Bx and/or clinical follow-up	24 (10–32)
Terakawa et al 2008[29]	Japan	1995–2006	26	1	Retrospective	ND	Suspected recurrence or radiation necrosis by clinical symptoms and MRI	MET	None	MRI or CT	36 (Tx)	Bx or clinical follow-up >6 mo by MRI	ND
Nakajima et al 2009[30]	Japan	1995–2008	18	1	Retrospective	ND	Suspected recurrence or radiation necrosis	MET	MRS	MRI	15 (4–80) (Tx)	Bx or clinical follow-up >6 mo by MRI	67[b]
Spence et al 2009[40]	US	ND	19	1	Retrospective	ND	To differentiate tumor recurrence from radiation necrosis	FDG, FLT	None	Enhanced MRI	24 (2–120) (Tx)	Bx or clinical follow-up by MRI	14 (3–56)
Jeong et al 2010[31]	South Korea	2003–2009	32	1	Retrospective	ND	Suspected recurrence by MRI	FLT, FET	None	Enhanced MRI	13[b] (1–114) (Tx)	Bx or clinical follow-up by MRI	ND
Ozsunar et al 2010[32]	US	ND	30	1	Retrospective	ND	Suspected recurrence or necrosis by MRI	FDG	MRI-DSCE-CBV, MRI-ASL	MRI	>6 mo[e]	Bx or clinical follow-up >12 mo	ND
Prat et al 2010[33]	Spain	ND	26	1	Retrospective	ND	Suspected recurrence, histologic upgrading, or radiation necrosis by MRI	FDG	MRS, pMRI	Enhanced MRI	ND	Bx or clinical follow-up >5 mo by MRI	5.6[b,c] 14.7[b,c]
Santra et al 2012[41]	India	2006–2008	90	1	Prospective	ND	Clinical suspicion of recurrence	FDG	None	None	ND	Bx or clinical follow-up ≥6 mo by imaging	ND

continued

ON-LINE TABLE 1, continued

Study	Country	Study Period (yr)	Patient (No.)	Institution (No.)	Design	Clinical Context	Indication	Tracer	Comparator Imaging Tests	Prior Imaging Tests	Median Time (from Dx/Tx) to Imaging (range) (mo)	Reference Standard	Median Follow-Up after PET (range) (mo)
High-grade only													
Valk et al 1988[34]	US	ND	32	1	Retrospective	ND	Worsening of symptoms or CT findings	FDG	None	CT	11 (3–27) (Tx)	Bx or clinical follow-up	8 (2–37)
Van Tassel et al 1995[35]	US	1988–1992	10	1	Retrospective	Post 1st-line	New enhancing parenchymal lesions by MRI	FDG	None	Enhanced MRI or CT	ND	Bx only	NA
Tsuyuguchi et al 2004[36]	Japan	ND	11	1	Retrospective	Post 1st-line	Suspected recurrence or necrosis	MET	None	MRI	7	Bx or clinical follow-up >5 mo by MRI	7 (5–12)
Miyashita et al 2008[37]	Japan	2002–2006	10	1	Retrospective	Post 1st- and 2nd-line	Suspected recurrence or progression by MRI	BPA	None	Enhanced MRI[l]	ND	Bx or clinical follow-up by MRI[l]	ND
Dandois et al 2010[38]	Belgium	ND	28	1	Retrospective	ND	Suspected recurrence or necrosis	MET	pMRI	Enhanced MRI, FLAIR MRI, DWI	ND	Bx or clinical follow-up including PET	13[b] (3–40)
Kim et al 2010[39]	South Korea	2001–2007	10	1	Retrospective	Post 1st-line	Newly enhanced lesions by MRI, without clinical evidence of recurrence	FDG, MET	pMRI	MRI	ND	Bx or clinical follow-up >12 mo	6.5 (6–10)[i] 28 (18–50)[c]

Note:—ASL indicates arterial spin-labeling; DSCE, dynamic susceptibility contrast-enhanced; BPA, 18F-boronophenylalanine; pMRI = perfusion MR imaging; Bx, biopsy; Dx, diagnosis; IMT, 123I-alpha-methyl-tyrosine; NA, not applicable; ND, no data; Tx, therapy.

[a] Only living patients.

[b] Mean.

[c] Nonrecurrent patients.

[d] Conventional MRI was compared.

[e] Patients followed up without biopsy.

[f] Biopsied patients.

[g] The Macdonald Criteria (Macdonald D, Cascino T, Schold SJ, et al: Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol* 1990;8:1277–80) were used.

[h] Stable disease required no changes by MRI >3 months for high-grade glioma and >6 months for low-grade glioma.

[i] After completion of proton beam therapy.

[j] Recurrent patients.

[k] Previously performed BPA-PET was also used.

[l] Stable disease required no changes by MRI for >4 months.

ON-LINE TABLE 2: Patient and therapy characteristics of studies of positron-emission tomography to differentiate recurrence from treatment-related necrosis in treated glioma

Study	Patient (No.)	Median Age (yr)	Male (%)	Histology (%)	Tumor Location (%)	Treatment (%)	Use of TMZ (%)
Any grades							
Janus et al 1993[16]	50	39 (15–66)	64	LG: 20; HG: 80	ND	LG: Surg + RTx + Cx (40), Surg + RTx (40), RTx + Cx (10), Surg alone (10); HG: Surg + RTx + Cx (73), Surg + RTx (15), RTx + Cx (8), RTx alone (3), none (3)	0
Kahn et al 1994[17]	17	38 (26–57)	52[a]	LG: 29; HG: 71	ND	ND	0
Nelson et al 1997[18]	19	47 (26–70)	68	LG: 16; HG: 84	ND	LG: RTx (34) HG: RTx (88)	0
Ricci et al 1998[19]	28	46[b] (27–70)[a]	55[a]	LG: 25; HG: 75	ND	HG/LG: Surg + RTx ± Cx	0
Sonoda et al 1998[20]	10	36 (21–68)	60	LG: 50; HG: 50	ND	HG/LG: Surg + RTx + Cx (90), RTx + Cx (10)	0
Bader et al 1999[21]	30	50 (32–70)	73	LG: 40; HG: 60	ND	HG/LG: Surg, RTx, or Surg + RTx	0
Thompson et al 1992[2]	15	52[b] (25–72)	ND	ND	ND	HG/LG: RTx + Cx (93), RTx alone (7)	0
Belohlávek et al 2002[23]	29	ND (17–65)	72	LG: 10; HG: 90	ND	ND	0
Pöpperl et al 2004[24]	53	ND	53	LG: 19; HG: 81	ND	HG/LG: Surg (83), RTx (94), CTx (40), IRS (13), RIT (17)	0
Van Laere et al 2005[25]	30	40 (11–69)	70	LG: 50; HG: 50	Supratentorium: 93; infratentorium: 7	LG: Surg + RTx (47), RTx (20), Cx (20), Surg + RTx + Cx (7), RTx + Cx (7); HG: Surg + RTx (73), RTx (20), RTx + Cx (7)	ND
Rachinger et al 2005[26]	36	45[b] (26–75)[a]	51[a]	LG: 24; HG: 76[c]	ND	HG/LG: "conventional" + RIT or paclitaxel	0
Gómez-Río et al 2008[27]	76	48[b] ± 16[d]	57	LG: 42; HG: 58	ND	HG/LG: Surg + RTx	0
Mehrkens et al 2008[28]	31	46[b] (29–65)	55	LG: 55; HG: 45	Supratentorium: 100	LG: IRS (69), Surg (50), RTx (50), Cx (31); HG: Surg + RTx (100), Cx (43), IRS (14), RIT (7), IPDT (7)	ND
Terakawa et al 2008[29]	26	54 (14–83)[a]	60[a]	LG: 23; HG: 77	ND	HG/LG: RTx ± SRS	0
Nakajima et al 2009[30]	18	45[b] (14–67)	67	LG: 22; HG: 78	ND	HG/LG: RTx + Cx (100)	ND
Spence et al 2009[40]	19	46 (19–67)	68	LG: 16; HG: 84	Supratentorium: 100	LG: RT (33), l RT + Cx (67); HG: RT (13), RTx + Cx including TMZ (87)	74
Jeong et al 2010[31]	26	ND	58	LG: 15; HG: 85	Lobar: 69; deep: 19; multicentric: 4	GBM: Surg + RTx + TMZ (100); anaplastic tumors: Surg + RTx + BCNU (100); LG: Surg alone (100)	42
Ozsunar et al 2010[32]	32	47[b] (32–68)	38	LG: 31; HG: 69	ND	LG: Surg (10), Surg + Cx (30), Surg + Cx + RTx (60); HG: Surg (14), Surg + Cx (23), Surg + Cx + RTx (50), Surg + RTx (14)	ND
Prat et al 2010[33]	30	42[b] (20–69)	73	LG: 23; HG: 77	ND	LG/HG: Surg + RTx + PBRT ± Cx (100)	ND
Santra et al 2012[41]	90	37[b] (12–68)	73	LG: 40; HG: 60	Supratentorium: 94; infratentorium: 6	LG/HG: Surg + RTx (53), Surg + RTx + Cx (38), Surg or RTx (9)	ND
High-grade only							
Valk et al 1988[34]	32	ND	ND	HG: 100	ND	HG: Surg/Bx + RTx + Cx (75), Surg/Bx + RTx (25)	0
Van Tassel et al 1995[35]	10	ND	ND	HG: 100	ND	HG: RTx + Cx (100)	0
Tsuyuguchi et al 2004[36]	11	35 (23–62)	72	HG: 100	Supratentorium: 91; infratentorium: 9	HG: Surg + RTx + SRS + Cx (100)	0
Miyashita et al 2008[37]	10	ND	ND	HG: 100	ND	HG: Surg + RTx + BNCT (100)	0
Dandois et al 2010[38]	28	51[b] (25–74)	57	HG: 100	ND	HG: RTx + TMZ (18), Surg + RTx + TMZ (82)	100
Kim et al 2010[39]	10	46[b] (31–66)	80	HG: 100	Supratentorium: 90; infratentorium: 10	HG: Surg + RTx (100), PCV (20), ACNU + CDDP (20), TMZ (50)	50

Note:—ACNU indicates nimustine; BCNU, carmustine; BNCT, boron neutron capture therapy; CDDP, cisplatin; Cx, chemotherapy; GBM, glioblastoma multiforme; HG, high-grade; IPDT, interstitial photodynamic therapy; IRS, interstitial radiosurgery; LG, low-grade; ND, no data; PBRT, proton beam radiation therapy; PCV, procarbazine, lomustine, vincristine; RIT, radioimmunotherapy; RTx, radiation therapy; Surg, surgery; TMZ, temozolomide; Bx, biopsy; SRS, stereotactic radiosurgery.

[a] Whole included patients, some of whom had irrelevant histologies.

[b] Mean.

[c] Whole included patients, some of whom were evaluated with PET for an irrelevant purpose.

[d] SD.

ON-LINE TABLE 3: PET characteristics of studies of positron-emission tomography to differentiate recurrence from treatment-related necrosis in treated glioma

Study	PET Tracer	Type of PET Scanner	Model (Maker)	Preparation (Time, hr)	Administered PET Tracer Activity (MBq)	Time of Scanning after Injection (min)	Scan Time (min)	Attenuation Correction	Image Reconstruction Method
Any grades									
Janus et al 1993[16]	FDG	PET camera	Posicam 6.5 (Positron, Westmont, Illinois)	ND	185–370	ND	~20	Performed	ND
Kahn et al 1994[17]	FDG	PET camera	GE-4096 plus PET system (GEMS, Milwaukee, Wisconsin)	Fasting (4)	370	0	45	Performed	ND
Nelson et al 1997[18]	FDG	PET camera	ECAT Exact HR (Siemens, Erlangen, Germany)	ND	370	40	30	Performed	ND
Ricci et al 1998[19]	FDG	PET camera	GE-4096 (GEMS)	ND	370	30	25	Performed	FBP
Sonoda et al 1998[20]	MET	PET camera	PT931 (CTI, Largo, Maryland)	ND	111–555	30	10	Performed	ND
Bader et al 1999[21]	FDG	PET camera	ECAT Part1 (CTI/Siemens)	Fasting (≥12)	200	ND	ND	Performed	FBP
Thompson et al 1992[2]	FDG	ND	ND	ND	ND	ND	ND	ND	ND
Belohlávek et al 2002[23]	FDG	PET camera	ECAT Exact HR (Siemens)	Fasting (6)	3[a]	35–40	15	Performed	OSEM
Pöpperl et al 2004[24]	FET	PET camera	ECAT Exact HR+ (Siemens)	Fasting (≥6)	180	30	30	Performed	FBP
Van Laere et al 2005[25]	FDG, MET	PET camera	ECAT Exact HR (Siemens)	Fasting (≥12)	150 (FDG), 220 (MET)	30 (FDG), 20–40 (MET)	20 (FDG), 20 (MET)	Performed	FBP
Rachinger et al 2005[26]	FET	PET camera	ECAT Exact HR+ (Siemens)	Fasting (≥6)	180	0	60	Performed	FBP
Gómez-Río et al 2008[27]	FDG	PET camera	ECAT Exact47 (Siemens)	Fasting (6)[b]	185	45	ND	ND	OSEM
Mehrkens et al 2008[28]	FET	PET camera	ECAT Exact HR+ (Siemens)	Fasting (≥6)	180	0	60	Performed	FBP
Terakawa et al 2008[29]	MET	PET camera	Headtome IV (Shimadzu)	Fasting (ND)	6[a]	20	10	Performed	ND
Nakajima et al 2009[30]	MET	PET camera	Headtome V (Shimadzu)	ND	200–550	20	10	Performed	FBP
Spence et al 2009[40]	FDG, FLT	PET camera	GE Advanced PET tomography (GEMS)	Fasting (FDG)	3.7[a] (FDG), 2.7[a] (FLT)	75 (FDG), 0 (FLT)	15 (FDG), 90–120 (FLT)	Performed	ND
Jeong et al 2010[31]	FLT, FET	PET camera, PET/CT[c]	ECAT Exact HR+ (Siemens), Biograph 6 PET/CT scanner (Siemens)	ND	370	30	20 (PET), 10 (PET/CT)	Performed	OSEM
Ozsunar et al 2010[32]	FDG	PET camera	PC-384 or PC-4096 (Scanditronix, Uppsala, Sweden)	ND	185–370	0	45 minutes	Performed	FBP
Prat et al 2010[33]	FDG	ND	ND	ND	ND	ND	ND	ND	ND
Santra et al 2012[41]	FDG	PET/CT	Biograph 2 PET/CT scanner (Siemens)	Fasting (4)	370	45–60	6–10	Performed	OSEM
High-grade only									
Valk et al 1988[34]	FDG, ^{82}Rb	PET camera	Donner 280-Crystal Positron Ring (Lawrence Berkeley Laboratory, Berkley, California)	ND	370 (FDG), 555 (^{82}Rb)	0 (FDG), 0 (^{82}Rb)	45 (FDG), 5 (^{82}Rb)	Performed	ND
Van Tassel et al 1995[35]	FDG	ND	ND	ND	185–370	ND	ND	ND	ND
Tsuyuguchi et al 2004[36]	MET	PET camera	Headtome IV (Shimadzu)	Fasting (4)	370	20	10	Performed	ND
Miyashita et al 2008[37]	BPA	PET camera	Headtome III (Shimadzu)		3.7–5.55[a]	0	60	ND	ND
Dandois et al 2010[38]	MET	PET camera	HR961 (CTI/Siemens)	ND	740	15	20	Performed	FBP
Kim et al 2010[39]	FDG, MET	PET camera	ECAT Exact 47 (Siemens)	Fasting (6)	370–555 (FDG), 550–740 (MET)	40 (FDG), 10 (MET)	20 (FDG), 20 (MET)	Performed	ND

Note:—BPA indicates 18F-boronophenylalanine; FBP, filtered back-projection; ND, no data; OSEM, ordered subset expectation maximization; GEMS, GE Healthcare; ^{82}Rb, rubidium-82.

[a] Administered activity per kilogram of body weight.

[b] Fasting blood glucose <120 mg/dL was required for inclusion.

[c] Five of 32 patients were evaluated with PET/CT.

ON-LINE TABLE 4: Diagnostic criteria of positron-emission tomography to differentiate recurrence from treatment-related necrosis in treated glioma

Study	PET Drug	Method	Visual Assessment		Quantitative Assessment, Cutoff Value	Referent Baseline Scan	No. of Interpreters	Experience of Interpreters
			Positive Criteria	Negative Criteria				
Any grades								
Janus et al 1993[16]	FDG	Visual assessment	Increase in activity relative to the contralateral hemisphere or adjacent area suggestive of tumor progression	Decreased activity	–	ND	2	ND
Kahn et al 1994[17]	FDG	Visual assessment using a grading scale[a]	Increased FDG uptake relative to the immediately adjacent tissue	Markedly reduced or absent FDG uptake	–	ND	3	Experienced nuclear medicine specialists
Nelson et al 1997[18]	FDG	Visual assessment using a grading scale[b]	ND	ND	–	ND	ND	Experienced (>15 year) interpreters
Ricci et al 1998[19]	FDG	Visual assessment using a grading scale[c]	Hypermetabolic relative to contralateral white matter grade 2 or 3[c]	Activity less than or equal to white matter grade 0 or 1[c]	–	ND	ND	CAQ certified neuroradilogist
Sonoda et al 1998[20]	MET	Visual assessment, quantitative assessment using tumor-to-normal gray matter ratio (T/N)[d]	Increased uptake	Normal or decreased uptake	ND	ND	ND	ND
Bader et al 1999[21]	FDG	Visual assessment	ND	ND	–	ND	≥2	ND
Thompson et al 1992[2]	FDG	ND	ND	ND	–	ND	ND	ND
Belohlávek et al 2002[23]	FDG	Visual assessment	Clearly apparent focal accumulation of FDG	No focally enhanced activity	–	ND	ND	ND
Pöpperl et al 2004[24]	FET	Quantitative assessment using SUVmax, quantitative assessment using SUVmax/background ratio[e]	–	–	2.2 (SUVmax), 2.0 (SUVmax/BG)	ND	ND	ND
Van Laere et al 2005[25]	FDG, MET	Quantitative assessment using tumor to contralateral cortical background uptake ratio	–	–	0.8 (FDG), 2.2 (MET)	ND	2	ND
Rachinger et al 2005[26]	FET	Quantitative assessment using SUVmax	–	–	2.2	ND	ND	ND
Gómez-Río et al 2008[27]	FDG	Visual assessment	Unexplainable metabolic activity, increased FDG uptake lesion relative to immediately adjacent tissue or closest adjacent white matter in one or more transaxial sections	ND	–	ND	ND	ND
Mehrkens et al 2008[28]	FET	Quantitative assessment using SUVmax/background ratio[e]	–	–	2.0	ND	ND	ND
Terakawa et al 2008[29]	MET	Quantitative assessment using SUVmax, quantitative assessment using SUVmean, quantitative assessment using lesion to normal tissue ratio (L/N) max[f], quantitative assessment using L/Nmean[f]	–	–	1.58 (L/Nmean)	ND	2	Experienced nuclear medicine radiologists
Nakajima et al 2009[30]	MET	Quantitative assessment using tumor to normal gray matter ratio (T/N)	–	–	2.0	ND	ND	ND
Spence et al 2009[40]	FDG, FLT	Visual assessment using a grading scale, quantitative assessment using SUVmean, SUVmax; tumor to normal cortex (T/C) or white matter ratio (T/WM) (FDG only); and kinetic model (FLT only)	ND	ND	ND	ND	2	Experienced nuclear medicine specialists
Jeong et al 2010[31]	FLT, FET	Quantitative assessment using SUVmax, quantitative assessment using lesion to normal ratio (LNR)[g]	–	–	Any grades: 0.44 (SUVmax, FLT), 1.66 (SUVmax, FET); 3.0 (LNR, FLT), 2.18 (LNR, FET), HGG: 0.8 (SUVmax, FLT), 1.66 (SUVmax, FET); 3.0 (LNR, FLT), 2.46 (LNR, FET)	ND	ND	ND
Ozsunar et al 2010[32]	FDG	Visual assessment	ND	ND	–	ND	2	Board-certified neuroradiologists
Prat et al 2010[33]	FDG	Semiquantitative assessment comparing pathologic images with those on the contralateral side[h]	ND	ND	–	ND	ND	ND

continued

ON-LINE TABLE 4, continued

Study	PET Drug	Method	Visual Assessment		Quantitative Assessment, Cutoff Value	Referent Baseline Scan	No. of Interpreters	Experience of Interpreters
			Positive Criteria	Negative Criteria				
Santra et al 2012[41]	FDG	Visual assessment	A definite lesion on CT images (hypermetabolic/iso-metabolic/ hypometabolic on PET images) or an increased focal FDG uptake without any clearly discernible lesion on CT	ND	–	ND	2	Experienced nuclear medicine physicians
High-grade only								
Valk et al 1988[34]	FDG	Visual assessment	Activity greater than or equal to that of the adjacent brain	Activity less than that of the adjacent brain	–	ND	2	ND
Van Tassel et al 1995[35]	FDG	Visual assessment	Hypermetabolic tumor	ND	–	ND	ND	ND
Tsuyuguchi et al 2004[36]	MET	Visual assessment, quantitative assessment using SUVmean, quantitative assessment using tumor lesion to normal ratio (Tmean/Nmean)[i]	ND	ND	ND	ND	2	Experienced nuclear medicine physicians
Miyashita et al 2008[37]	BPA	Quantitative assessment using lesion to normal ratio (L/N)[i]	–	–	2	Performed partially	ND	ND
Dandois et al 2010[38]	MET	Visual assessment	ND	ND	–	ND	ND	Nuclear medicine physicians
Kim et al 2010[39]	FDG, MET	Visual assessment, quantitative assessment using lesion to reference area ratio (Lmax/Rmax)[k]	ND	ND	1.45 (FDG), 2.64 (MET)	ND	ND	ND

Note:—BPA indicates 18F-boronophenylalanine; CAQ, certificate of added qualification; ND, no data; SUV, standard uptake value; Lmax, maximum uptake in tumor lesion; R/max, maximum uptake in reference area; LNR, lesion to normal ratio; Tmean, mean uptake in tumor lesion; Nmean, mean uptake in normal brain; T/N, tumor to normal; BG, background; SUVmax, maximum standardized uptake value; SUVmean, mean standardized uptake value; T/WM, tumor to white matter ratio; HGG, high-grade glioma.

[a] Grade 1 = totally absent, grade 2 = slightly less uptake than surrounding area, grade 3 = same uptake as surrounding area, grade 4 = slightly to moderately increased uptake compared with surrounding area, grade 5 = markedly increased uptake.

[b] Grade 0 = intensity less than that of white matter, grade 1 = intensity similar to that of white matter, grade 2 = intensity between white matter and gray matter, grade 3 = intensity similar to gray matter, grade 4 = intensity higher than gray matter.

[c] Grade 0 = no applicable metabolic uptake, grade 1 = similar to normal contralateral white matter, grade 2 = between contralateral white matter and gray matter, grade 3 = equal to or over gray matter.

[d] Differential absorption ratio defined as the product of tissue radioactivity and the patient's body weight divided by the administered radioactivity of MET was used to estimate T/N ratio.

[e] Background (BG) was defined as the mean uptake of 70% and 80% of isocontour regions mirrored to the contralateral (ie, non-tumor-bearing) hemisphere.

[f] L/Nmean was defined as the SUVmean of the lesion divided by the SUVmean of the contralateral normal frontal-lobe gray matter. L/Nmax was defined as the SUVmax of the lesion divided by the SUVmean of the contralateral normal frontal-lobe gray matter.

[g] Normal brain parenchyma, usually in the contralateral normal frontal cerebral cortex was used as the reference.

[h] Visual assessment (inferred).

[i] Normal gray matter in the contralateral frontal lobe was used as the reference.

[j] Normal brain area in the contralateral brain lobe was used as the reference.

[k] Corresponding area in the contralateral brain lobe was used as the reference.

ON-LINE TABLE 5: Quality assessment of included studies

Study	1 Spectrum Bias	2 Inclusion Criteria	3 Reference Standard	4 Partial Verification Bias	5 Differential Verification Bias	6 Incorporation Bias	7 Index Test	8 Reference Standard	9 Test Review Bias	10 Diagnosis Review Bias	11 Treatment Paradox	12 Clinical Data	13 Uninterpretable or Intermediate Results	14 Withdrawal
Any grades														
Janus et al 1993[16]	N	Y	Y	Y	U	Y	Y	Y	Y	U	N	Y	N	N
Kahn et al 1994[17]	N	Y	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	N
Nelson et al 1997[18]	N	U	N	Y	U	U	Y	N	U	U	U	Y	Y	N
Ricci et al 1998[19]	N	Y	N	N	Y	Y	Y	Y	U	U	U	Y	Y	Y
Sonoda et al 1998[20]	N	U	Y	Y	U	U	Y	Y	U	U	U	U	N	N
Bader et al 1999[21]	Y	U	N	Y	Y	Y	Y	Y	U	U	Y	U	Y	N
Thompson et al 1992[2]	N	Y	N	N	Y	Y	N	Y	U	U	U	U	N	N
Belohlávek et al 2002[23]	N	U	U	Y	U	U	Y	N	Y	U	U	N	Y	N
Pöpperl et al 2004[24]	N	U	Y	Y	U	Y	Y	Y	U	U	U	U	N	N
Van Laere et al 2005[25]	N	U	U	Y	U	U	Y	N	U	U	U	U	N	Y
Rachinger et al 2005[26]	N	U	Y	Y	Y	Y	Y	Y	U	Y	U	U	N	N
Gómez-Río et al 2008[27]	Y	Y	Y	Y	U	Y	Y	Y	U	U	U	Y	N	N
Mehrkens et al 2008[28]	Y	Y	Y	Y	U	Y	Y	Y	U	Y	U	Y	N	N
Terakawa et al 2008[29]	N	Y	Y	Y	U	Y	Y	Y	U	U	Y	Y	N	Y
Nakajima et al 2009[30]	N	U	U	Y	U	U	Y	N	U	U	U	Y	N	N
Spence et al 2009[40]	N	Y	Y	Y	U	Y	Y	Y	U	U	Y	U	Y	N
Jeong et al 2010[31]	N	Y	Y	Y	U	Y	Y	Y	U	U	U	Y	N	N
Ozsunar et al 2010[32]	N	Y	Y	Y	U	U	Y	Y	U	Y	U	U	N	N
Prat et al 2010[33]	N	Y	Y	Y	U	Y	N	Y	U	U	U	U	N	N
Santra et al 2012[41]	Y	Y	Y	Y	U	Y	Y	Y	Y	U	U	N	N	N
High-grade only														
Valk et al 1988[34]	N	Y	Y	Y	U	U	Y	Y	U	U	N	U	N	N
Van Tassel et al 1995[35]	N	Y	N	N	Y	Y	N	Y	U	U	U	U	N	Y
Tsuyuguchi et al 2004[36]	N	U	Y	Y	U	U	Y	Y	U	U	U	U	N	N
Miyashita et al 2008[37]	N	U	Y	Y	U	Y	Y	Y	U	U	U	Y	N	N
Dandois et al 2010[38]	N	U	N	Y	U	N	Y	N	U	N	Y	U	N	N
Kim et al 2010[39]	N	Y	Y	Y	U	Y	Y	Y	U	U	U	Y	N	N

Note:—Y indicates yes (relevant information reported or bias avoided); N, no (relevant information not reported or bias not avoided); U, unclear (insufficient reporting or avoidance of bias unclear).