

Research Digest

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Chemotherapy Prevents Local Recurrence But Doesn't Prolong Survival In Patients With Rectal Cancer

Preoperative radiotherapy is a standard treatment option for patients with stage T3 or T4 rectal cancers. The role of chemotherapy is less clear. A clinical trial found that additional chemotherapy based on fluorouracil had no impact on patients' survival, but it did help to prevent local recurrences whether it was given before or after surgery. Four groups of patients (Total 1011) had preoperative radiotherapy plus either preoperative chemotherapy, postoperative chemotherapy, both, or neither. About 65% of them survived for five years regardless of their assigned treatment. But patients who had no chemotherapy at all were more likely to have a local recurrence (17%) than the other three groups (8.7%, 9.6%, and 7.6%, $P = 0.002$). The timing of the chemotherapy didn't seem to matter, except that patients who had their treatment before surgery were more likely complete it. Less than half the patients who were meant to have postoperative chemotherapy managed to complete the course specified by the protocol of the trial. Over a quarter failed to start, mostly because they had postoperative complications, disease progression, or simply said no. The authors conclude that preoperative chemotherapy with fluorouracil is probably worth considering for some patients.

N Engl J Med 2006; 355: 1114-1123

Children with Otitis Media Do Well with Optional Antibiotics

American doctors often prescribe antibiotics for children with acute otitis media, even though there is good evidence from Europe that a "wait and see" policy can work just as well. They now have their own culturally specific evidence from a large trial set

in an urban emergency department in New Haven, Connecticut. Children whose parents were given a delayed prescription to fill in if their child wasn't better (or got worse) over the next two days had similar short and medium term outcomes as children who were given antibiotics immediately. Immediate antibiotics made no difference to the children's fever, use of analgesics for ear pain, or rate of otalgia after a few days or two weeks. Antibiotics did not prevent vomiting, or further visits to a doctor. Children given antibiotics immediately had a few hours less ear pain over the first few days (2.0 days v 2.4 days; $P = 0.02$), but they also had more diarrhoea (23%, 31/133 v 8%, 10/132 $P < 0.001$). Most importantly though, delayed prescriptions reduced parents' use of antibiotics from 87% to 38%, a significant effect that can only help in the fight against antibiotic resistance. The parents in this setting seemed willing to try the delayed prescription approach, and those that managed without antibiotics were more likely to say they would do without next time (63% v 28%, $P < 0.001$).

JAMA 2006; 296: 1235-1241

Green Tea is Associated with Longer Life for Japanese Adults

Many claims have been made about the potential benefits of green tea. Research in humans has been inconsistent, possibly because the studies have been too small to find a modest effect. The largest study so far reports that drinking several cups a day is associated with a reduced risk of death, and a reduced risk of cardiovascular death, particularly stroke. The same study, which included over 400 000 Japanese adults, found no evidence that green tea can help prevent cancer deaths. Green tea is one of the most popular drinks in Japan and most of the participants regularly drank at least one small cup a

day. A Japanese cup measures about 100 ml. The inverse associations between green tea and all cause and cardiovascular mortality were strongest in women and were significant for those drinking three or more cups a day (hazard ratio for cardiovascular mortality 0.69, 95% CI 0.52 to 0.93 for three to four cups and 0.53 to 0.90 for five or more). In men, the associations were significant only for those who drank five or more cups a day, and even then the benefit seemed smaller. Green tea contains polyphenols which scavenge free radicals among other things. So a link with good cardiovascular health is biologically plausible. Ultimately though, only prospective clinical trials can establish for certain whether or not green tea can prolong your life.

JAMA 2006; 296: 1255-1265

Young Women with Hepatitis C are More Likely to Die from Drugs than from Liver Disease

Between 1990 and 2002, 117 547 new cases of hepatitis B or C were notified to the New South Wales state health department in Australia, including 2604 new cases of mixed infection with both viruses. All three groups had a higher mortality rate than the general population in a recent study, and by linking the notifiable diseases database with the Australian death register, researchers have pieced together a comprehensive picture of what they died of. Perhaps unsurprisingly, deaths coded as viral hepatitis and its sequelae dominated the picture, with standardized mortality ratios between about 36 (for patients with hepatitis B) and 113 (for patients with both viruses). Similarly, liver related mortality was 12 to 33 times greater than in the general population—liver cancer accounting for the greatest number of excess deaths in people with hepatitis B. The group with hepatitis C, however, was characterized by a large excess of drug related deaths, presumably because intravenous injection of illegal drugs is a leading cause of hepatitis C worldwide. With a standardized mortality ratio of nearly 20, patients in this group were significantly more likely to die from drug use than from the ensuing liver disease. The link between hepatitis C and a drug related death was particularly strong in young women aged between 15 and 40 years.

Lancet 2006; 368: 938-945

A New Pill for Multiple Sclerosis Deserves Further Study

An oral treatment for relapsing multiple sclerosis looked promising in an early clinical trial. For six months 255 patients took the drug fingolimod or a matching placebo, during which time the drug significantly reduced the number of brain lesions, as measured by magnetic resonance imaging, and reduced the risk of relapse. In a six-month extension to the core trial, patients who switched from placebo to fingolimod also improved. The trial tested two doses that seemed to work equally well. Safety remains an issue, however. Fingolimod is an immunomodulator that acts mainly on lymphocytes, locking them in lymph nodes and reducing the peripheral lymphocyte count. In this study, lymphocyte counts fell quickly by about 70% to 80% in both treated groups. Upper respiratory tract infections were common, particularly in patients taking the higher dose, and there were two serious infections—one patient developed facial herpes zoster and another developed enterocolitis. Fingolimod was also associated with transient reduction in heart rate, asymptomatic abnormalities in liver enzymes, and one case of posterior reversible encephalopathy syndrome (a serious abnormality in the occipital region of the brain that causes temporary blindness, dysarthria, and ataxia).

N Engl J Med 2006; 355: 1124-1139

Redistributing Wealth is Good for Health

Politicians set the public health agenda according to the political aspirations and ideology of the party in power. So you might expect those aspirations and ideologies to have a measurable impact on the health of the population. Proving it is easier said than done, but teams from the United States, Canada, and Spain have made a start by showing that political ideologies encouraging the redistribution of wealth are associated with lower infant mortality, and to a lesser extent with longer life expectancy. They studied a group of developed countries belonging to the Organization for Economic Cooperation and Development, categorizing them according to dominant political tradition into social democracies, Christian democracies, liberal conservative

democracies, or dictatorships. Roughly speaking, these four traditions are in a descending hierarchy of wealth redistribution with social democracies, such as Norway and Sweden, at the top and dictatorships, such as those that ruled Spain and Portugal, at the bottom. The US and UK, as liberal conservative democracies are somewhere in the middle. The researchers found a clear and inverse correlation between infant mortality since 1972 and the length of time a country had been ruled by political parties that were for redistribution (correlation for 1996 - 0.747). Further analysis suggested that the benefits of egalitarian political ideology were mediated by policies encouraging full employment, generous public health expenditure, and universal social benefits.

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Fatty Fish may Protect Women from Renal Cancer

A diet rich in fatty fish such as salmon, herring, and mackerel seems to be associated with a lower risk of renal cell carcinoma in women, according to a large prospective cohort study from Sweden. Women in the cohort who ate fatty fish at least once a week were 44% less likely to develop renal cancer over a 15 year follow-up than women who ate no fatty fish (adjusted rate ratio 0.56, 95% CI 0.35 to 0.91). The researchers found no link between incidence of renal cancer and any other type of fish or seafood including the lean fish types such as cod and tuna. The study included over 60 000 Swedish women aged between 40 and 76 who filled in a food frequency questionnaire at baseline between 1987 and 1990. A subgroup of 36 664 filled in a second questionnaire 10 years later, which allowed the researchers to assess the impact of consistent and long term consumption of fatty fish. The risk reduction was an even bigger 74% (rate ratio 0.26, 0.1 to 0.67), even after adjustment for a long list of confounding factors including age, education, body mass index, other aspects of diet, smoking, alcohol intake, hypertension, and diabetes.

JAMA 2006; 296: 1371-1376

Syncope is the Best Predictor of Cardiac Arrest or Death in Young People with Long QT Syndrome

Adolescents with hereditary long QT syndrome have an increased risk of ventricular arrhythmias and death. Catastrophic events are unpredictable, but a new study has identified three factors that might help doctors stratify these adolescents according to their risk: gender, the length of the QT interval, and history of syncope. They followed up 2772 patients on a US register between the ages of 10 and 20 years. Adolescents with a recent history of syncope had the highest risks of a life threatening arrhythmia or death before the age of 20, with a hazard ratio of 18.1 (95% CI 10.4 to 31.2, $P < 0.001$) for those with two or more syncopal attacks in the past two years. The two other factors were less important, but still significant. Boys had higher risks than girls, but only before the age of 12 years (hazard ratio 4.0, 95% CI 1.8 to 9.2, $P = 0.001$), as did those of either sex with a QTc of 530 ms (2.3, 1.6 to 3.3, $P < 0.001$). The effects of treatment are hard to assess from this kind of study, although β blockers did seem to help patients at very high risk. Overall, 45 of the 2772 patients in this study had sudden cardiac death before the age of 20. Another 81 were successfully rescued from cardiac arrest.

JAMA 2006; 296: 1249-1254

Diagnostic Errors are a Common Cause of Litigation among US Outpatients

In the outpatient setting, diagnostic mistakes that harm patients are common, complex, and deadly, according to a study of malpractice claims from four big US medical insurers. Missed, delayed, or wrong diagnoses that directly harmed the patient accounted for 59% (181/307) of all claims made by outpatients, and 30% resulted in death. Failure to take a proper history and examination, order the right test, or follow up the patient properly were the commonest diagnostic mistakes. Patients with cancer, usually breast or colorectal, were the commonest claimants. Primary care doctors were involved in 42% (76/181) of claims that alleged harm caused by diagnostic error. The science of patient safety outside hospitals is still in its infancy, but it's already clear that diagnostic

mistakes will be hard to eradicate. Doctors not thinking straight, making bad decisions, forgetting things, or not knowing them in the first place were a common theme in these claims—99% (179/181) cited one or more of these factors—but so were systems failures such as poor communication (30%, 55/181) and inadequate handovers (20%, 36/181). Most mistakes were the result of multiple breakdowns in the diagnostic process stretching over months or years and typically involving more than one healthcare worker. “The prospects for ‘silver bullets’ in this area seem remote,” say the authors.

Ann Int Med 2006; 145: 488-496

MRI Scans are a Useful Tool in Children with Cerebral Palsy

All children with cerebral palsy should undergo magnetic resonance imaging of their brain, say a European team of researchers. In their cross sectional study of 431 children, abnormalities revealed by the scans helped explain the pathological basis of the children’s disabilities and gave parents and doctors clues about what might happen in the future. White matter damage, including periventricular leucomalacia and periventricular haemorrhage, was the commonest abnormality in this mixed population of children (149/351, 42%). This kind of abnormality was associated with prematurity (three quarters of those with white matter damage were born early) and with bilateral spastic cerebral palsy. Children with the most extensive abnormalities had the most serious disabilities. Possibly the most striking finding, however, was that 40% (158/400) of mothers with affected children said that they had had an infection during pregnancy: specifically, 19% reported a urinary tract infection, and 16% had taken antibiotics. For comparison, the authors examined routine data from one area of London and found an incidence of urinary tract infection during pregnancy of only about 3%. This is a lead worth following in the search for preventive strategies against cerebral palsy, say the authors.

JAMA 2006; 296: 1602-1608

Don’t Rush to Set up Rapid Response Teams for Deteriorating Inpatients

Rapid response teams that run to the patient’s bedside and rescue them from rapid deterioration, cardiac arrest, and death are one popular answer to the clamour for better patient safety in US hospitals. Influential organisations have already endorsed the idea in principle and are busy encouraging hospitals to implement rapid response programmes as a national lifesaving priority. But do they work? An article by three critical care experts says it’s much too early to tell and urges policy makers to pause for thought (and more research) before rushing headlong to buy an unproved intervention. Although 10 comparative studies have evaluated rapid response teams, only two are randomised trials, it says. The biggest trial, which included more than 100 000 patients, found that rapid response teams did not save lives or prevent cardiac arrests. So this complex intervention may not work at all. Even if it does, it may work no better than cheaper and easier options such as teaching the staff on general hospital wards to recognise the early signs of clinical deterioration. Rapid response teams sound like a good idea, but that’s all they are so far. US hospitals now risk diverting limited resources into an intervention that could prove little more than an expensive distraction. “Science, not frustration, should guide the development of national patient safety standards,” the article concludes.

JAMA 2006; 296: 1645-1647

“Lite” Version of Collaborative Care Fails Primary Care Patients with Depression

Collaborative care, usually with a nurse care manager, is an effective way to help the one in 10 primary care patients with depression. But it’s expensive, and economic considerations have stalled the dissemination of collaborative care in the US. In an attempt to find a less intensive but equally effective strategy, researchers developed a “lite” version of decision support that reduced patient contact with a care manager to a single, 15 minute telephone call but offered primary care doctors quarterly feedback on their patients’ progress. It didn’t work. In a cluster randomised trial, patients treated by doctors using

the programme got no better than patients treated with usual care. Both groups improved, but, at the end of 12 months, mean depression scores were still within the range associated with moderately severe depression (PHQ-9 scores of 10-15). The results were disappointing, not least because the slimmed down model significantly improved the quality of treatment. Compared with control patients, patients in the programme saw more mental health specialists, took more antidepressants, and took them for longer (76% took an antidepressant for at least 90 days v 62% of controls, $P = 0.008$). A linked editorial (pp 544-6) says that collaborative care management is still the way forward, but there is "no free lunch." Depressed people probably need at least 6-12 months of continuous follow-up by a care manager, coupled with triage and more intensive treatments for the sickest.

Ann Int Med 2006; 145: 477-487

Oral Misoprostol Reduces Postpartum Haemorrhage among Women in Rural India

Postpartum haemorrhage is the leading cause of maternal deaths in the developing world, where births happen at home and injectable uterotonic drugs such as oxytocin are often unavailable. Oral misoprostol is an affordable, widely available, and effective alternative, according to a placebo controlled clinical trial from rural India. Among low risk women attended at home or in a clinic by an auxiliary nurse midwife, misoprostol reduced the incidence of postpartum haemorrhage from 12.0% to 6.4% (relative risk 0.53 (95% CI 0.39 to 0.74)), reduced the incidence of severe bleeding from 1.2% to 0.2% (0.20 (0.04 to 0.91)), and reduced mean blood loss from 262.3 ml to 214.3 ml ($P < 0.0001$) compared with placebo. The 812 actively treated women took 600 µg of misoprostol within five minutes of delivery. The main side effects were shivering (52.2% v 17.3%) and fever (4.2% v 1.1%), which the authors consider an acceptable trade off in return for a safer delivery. A linked commentary (pp 1216-8) is cautiously optimistic about the future role of misoprostol as a lifesaving intervention for the world's most vulnerable women. But the authors warn against widespread and unregulated distribution until birth

attendants practising a long way from medical support know how to use the drug safely.

Lancet 2006; 368: 1248-1253

Tadalafil and Dexamethasone May Help Prevent High Altitude Pulmonary Oedema

People who climb rapidly to high altitudes risk acute mountain sickness, and a small minority gets potentially life threatening pulmonary oedema. There are few prophylactic treatments for either, so a team from Switzerland designed a clinical trial to test the vasodilator tadalafil, more commonly used for erectile dysfunction, and the corticosteroid dexamethasone in people with a predisposition to high altitude pulmonary oedema. The 29 participants were taken rapidly up an Italian mountain to an altitude of 4559 m, where they spent two nights. They began treatment with dexamethasone (8 mg twice daily), tadalafil (10 mg twice daily), or a placebo the day before their ascent. Both drugs helped prevent pulmonary oedema, which developed in seven of the nine people taking placebo, one of the eight people taking tadalafil, and none of the 10 people taking dexamethasone ($P < 0.05$ for both treatments v placebo). However, only dexamethasone helped prevent the much commoner acute mountain sickness. Both drugs controlled pulmonary artery pressures, which rise in response to hypoxia, significantly better than placebo. Tadalafil is a phosphodiesterase inhibitor that selectively dilates pulmonary arteries, so an effect on high altitude pulmonary oedema is biologically plausible. Exactly how dexamethasone works is still unclear, but it's the only drug so far that seems to prevent both acute mountain sickness and pulmonary oedema. This small, highly selective trial was not designed to look for side effects.

Ann Int Med 2006; 145: 497-506

Ophthalmologists Welcome One or Possibly Two New Treatments for Age Related Macular Degeneration

After searching for more than two decades researchers have finally found an effective treatment

for the severe form of age related macular degeneration. Ranibizumab is a monoclonal antibody directed against vascular endothelial growth factor, a protein that damages the retina by encouraging the growth of new blood vessels. In two large clinical trials, ranibizumab injected monthly into the vitreous humour halted the otherwise inevitable deterioration in eyesight associated with this disease and improved visual acuity by between one and two lines on a standard eye chart. Controls in both trials got worse: in the first trial they had placebo injections, and in the second they had photodynamic therapy with verteporfin. There were few serious complications in either trial. Ranibizumab was licensed for use in the US in June, but it's very expensive at nearly \$2000 a dose. Some ophthalmologists opt instead for ranibizumab's sister drug, bevacizumab, a larger version of the same monoclonal antibody. Bevacizumab is an intravenous treatment for cancer, so putting it into the eye is strictly off label. However, uncontrolled trials have suggested that it works, at about one tenth the cost of ranibizumab treatment. Two linked commentaries agree that it's now time for a head to head trial comparing the two (pp 1409-12, 1493-5).

N Engl J Med 2006; 355: 1419-31, 1432-1444

Azithromycin Works For Severe Cholera In Adults

The choice of antibiotics for treating cholera is primarily determined by the patterns of bacterial resistance and antibiotic toxicity. Tetracycline and its derivatives have for decades been the antibiotics of choice for treating cholera in adults, but they should be avoided in children and pregnant women. Erythromycin has often been used as an alternative, but, unlike tetracycline, it is not effective in a single dose. Azithromycin, a derivative of erythromycin, has less gastrointestinal toxicity than erythromycin and has been shown effective for treating cholera in children with a single dose. A recent equivalence trial of a single dose of azithromycin versus a single dose of ciprofloxacin, which had previously been shown to be effective for treating severe cholera in adults, showed that azithromycin was effective, but ciprofloxacin was not. The trial included almost 200

adult men with severe cholera who were treated in one hospital in Bangladesh in a period of a year and a half. Watery stools stopped within two days of giving azithromycin in more than 70% of patients. Ciprofloxacin was clinically effective in less than a third of people randomised to receive this drug. Similarly, azithromycin eliminated *Vibrio cholerae* from stool within two days from the start of treatment in almost 80% of people, compared with ciprofloxacin's 10%. The authors say that a single dose of ciprofloxacin may be too low a threshold for *V cholerae*, 01 strain.

N Engl J Med 2006; 354: 2452-2462

Maori People Get Poorer Hospital Care

Maori people, New Zealand's large indigenous minority, have previously been reported to have disadvantaged health status compared with the rest of the population. It is notoriously hard to distinguish, however, whether differences in the quality of care between ethnic groups result from discrimination by the system and staff or from other variations, such as access, appropriateness of treatment, or patients' choice. A recent retrospective study looked at preventable adverse events as the indicator of the quality of care in a nationally representative sample of people admitted in 1998 to New Zealand's public hospitals, which are funded by tax. The sample of more than 6500 patients was 15% Maori. Researchers excluded descendents of migrants from the nearby South Pacific area from their analysis. Admitted Maori patients were younger, had a different case mix (with more pregnancies and less chronic diseases), and were more likely to come from poor areas than non-Maori, non-South Pacific people. After adjustment for age, sociodemographic characteristics, and case mix, Maori patients had a slightly increased risk of in-hospital preventable adverse events than non-Maori, non-South Pacific people ($P = 0.05$). Deprivation score was not linked with occurrence of preventable adverse events and no evidence showed consistent differences between the groups in regard to possible causal factors for the disparities seen.

Lancet 2006; 367: 1920-1925

Naps and Coffee Help on Long Shifts

Even after many countries officially restricted the length of shifts that healthcare workers can work, shifts of 30 hours are not unusual. Research in real life settings into the effects of such long working hours on alertness and the quality of care is scarce. Research into interventions to reduce possible harm to patients and healthcare workers is also patchy. Two recent studies help fill the gap. In one study, 38 interns of internal medicine alternated for one year between two weeks of being able to find cover and take a nap on long shifts and two weeks of not having this option. With cover, the interns slept an average of 41 minutes longer per shift, reported less fatigue, and slept more efficiently compared with when cover was not provided. The study was underpowered, however, to assess the impact of napping on the quality of care. A small randomised crossover trial (pp 785-91) of night time driving showed that drinking coffee and taking naps did improve objectively measured driving performance as well as self reported fatigue and sleepiness. The study also found large variations between people in functioning when deprived of sleep and responding to coffee and naps.

Ann Intern Med 2006; 144: 792-798

Early Revascularisation Improves Survival

Early revascularisation, with either percutaneous coronary intervention or coronary artery bypass grafting, improves long term survival in patients with myocardial infarction complicated by cardiogenic shock due to ventricular failure. Previous studies showed that more people had survived a year after treatment. A multicentre randomised trial of 300 patients with follow-up lasting between one and 11 years, with a median of six years, compared overall survival in patients who had early revascularisation with patients who were initially stabilised by drugs. More than 30% of people randomised to early revascularisation survived until the end of follow-up, compared with less than 20% in the group stabilised by drugs (P = 0.02). In people who survived until they were discharged from hospital, almost two thirds

of those who received early revascularisation were alive at the end of follow-up, compared with less than half in the group stabilised by drugs. The authors argue that the data call for direct admission or early transfer of patients with myocardial infarction to centres with facilities for early revascularisation and advanced intensive care.

JAMA 2006; 295: 2511-2515

Type A Personality Traits are not Linked to Atherosclerosis

Much anecdotal experience and evidence from epidemiological studies has linked the risk of coronary heart disease to type A patterns of behaviour, characterised by time urgency and hostility. Prospective epidemiological studies had shown depression, anxiety, hostility, and anger to be associated with the increased risk of coronary heart disease. A recent study, however, failed to find a link between such personality traits and subclinical coronary atherosclerosis, assessed by coronary calcium that has been shown to predict cardiovascular events in previously asymptomatic people, independently of risk factors. A multiethnic population based cross sectional study included more than 6500 adults aged 45 to 84 with no history of cardiovascular disease. Coronary calcium, assessed by electron beam computed tomography of the chest, was not associated with anger, anxiety, depression, or chronic burden, which researchers measured using validated questionnaires. The accompanying editorial (pp 858-60) says that these findings rule out the possibility that atherosclerosis or cardiovascular events cause type A traits. It also seems evident that the traits do not cause atherosclerosis, but several biologically plausible explanations exist to support the notion that they still might cause cardiovascular events. The observed association between the traits and cardiovascular events are possibly confounded by still unknown characteristics, although the association has been shown to be independent of age, diabetes, smoking, lipids, obesity, physical activity, and baseline cardiovascular disease.

Ann Intern Med 2006; 144: 822-831

ACE Inhibitors Are Not Safe Throughout Pregnancy

Despite the lack of appropriate safety studies, angiotensin converting enzyme (ACE) inhibitors have been considered safe in the first trimester of pregnancy, although they are contraindicated in the second and third trimester because of the increased risk of fetopathy (which includes oligohydramnios, intrauterine growth retardation, hypocalvaria, renal dysplasia, anuria, renal failure, and death). A large retrospective cohort study has found a fourfold increased risk for congenital malformations of the cardiovascular and central nervous systems in babies whose mothers took ACE inhibitors in the first trimester of pregnancy, compared with mothers who did not receive treatment with antihypertensives. The researchers used the Medicaid data from Tennessee, which included nearly 30 000 infants born between 1985 and 2000 to mothers without diabetes. The cohort included 209 infants whose mothers were taking ACE inhibitors in only the first trimester of pregnancy and 203 infants whose mothers were taking other antihypertensive drugs, also in only the first trimester. The risk ratio of serious congenital malformations associated with ACE inhibitors, compared with mothers who did not take antihypertensive drugs, was 2.71 (95% CI 1.72 to 4.27). No increased risk was found for infants whose mothers were taking other antihypertensives.

N Engl J Med 2006; 354: 2443-2451

Whole Brain Radiation Before Stereotactic Radiosurgery for Metastases does not Improve Survival

Preceding stereotactic radiosurgery with whole brain radiation does not seem to improve survival or neurological functioning, compared with stereotactic surgery alone, in people with brain metastases. A recently published randomised controlled trial included 132 patients with one to four brain metastases of up to 3 cm in diameter and treated in 11 hospitals in Japan from 1999 to 2003. Median survival was 8 months in people who received whole brain radiation and 7.5 months in people who did not (P = 0.42). But the relapse rate after one year in people who did not receive whole brain radiation

was more than 75%, compared with less than 50% of patients who did. The study did not find any significant differences between the groups in preservation of systemic and neurological functioning, toxic effects of radiation, and causes of death. An accompanying editorial (pp 2535-6) discusses how both treatment regimens are a reasonable first choice for most people with four or fewer brain metastases, and the choice should take into account the patient's age, extracranial disease, and performance status.

JAMA 2006; 295: 2483-2491

Clopidogrel Plus Aspirin is Inferior to Oral Anticoagulation

People with atrial fibrillation, at high risk of stroke, are candidates for oral coagulation treatment, but only about half of them receive it, mostly because of the high risk of bleeding and the need for regular monitoring. Clopidogrel and aspirin are both antiplatelet drugs with different mechanisms of action, and, because aspirin alone reduces the risk of stroke in people with atrial fibrillation by 22% compared with placebo, the combination was thought to be a possible safer alternative to oral coagulation. A recent non-inferiority trial was stopped early, however, after a median follow-up of just over a year. Compared with people given oral anticoagulants, people randomised to clopidogrel plus aspirin had a 1.4-fold increased risk of first occurrence of stroke, non-central nervous system systemic embolus, myocardial infarction, or vascular death. Surprisingly, bleeding was less in the oral anticoagulants group than in the clopidogrel-aspirin group (2.2% v 9.4% a year). Differences were seen, however, between subgroups of people who were or were not receiving oral anticoagulants at the start of the study. The accompanying commentary (pp 1877-8) proposes that effects of the clopidogrel-aspirin combination in people naive to oral anticoagulants could be assessed in a new trial, but new developments in preventing stroke in people with atrial fibrillation are possibly going to come from oral direct thrombin blockers or oral factor Xa inhibitors, rather than antiplatelet drugs.

Lancet 2006; 367: 1903-1912

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