

Complications of anti-TNF therapies

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Anti-TNF drugs have revolutionized the treatment of rheumatoid arthritis (RA). Concerns about risks of infection and malignancy with these agents have led to scrutiny of available data. Patients with severe, active RA are more prone to infection and lymphoma than the general population, which confounds data interpretation. For both infection and cancer risk the data are contradictory, but suggest a) an increased risk of serious infection (~ twofold), b) that vigilance is required for tuberculosis and other granulomatous and intracellular infection when screening patients, as well as close monitoring thereafter, c) no overall increased cancer risk, but concerns regarding skin cancers, and possible greater risks for patients with prior tumors. Although the advantages of these drugs far outweigh their disadvantages, we cannot be complacent about monitoring patients on anti-TNF closely. Regular updates of analyses of observational databases for emerging problems are needed.

Antitumor necrosis factor (TNF) therapy has revolutionized the treatment of inflammatory arthritis. However, cytokine manipulation also has potentially deleterious consequences, because TNF- α has physiological and pathological roles. Currently, three TNF- α antagonists are available: two monoclonal antibodies (infliximab and adalimumab) and one soluble TNF- α receptor (etanercept), and all are generally well tolerated. Common side effects, including rashes and constitutional symptoms, are usually mild and self-limiting, and generally do not lead to drug discontinuation. Of greater concern are serious adverse events that may relate to TNF- α antagonists, particularly infections and tumor development. This review focuses on these possible complications, because their consequences may be devastating for the patient and could profoundly influence the use of these drugs. We concentrate on their use in rheumatoid arthritis (RA), because the greatest experience is in this disease. Concerns over major adverse events with anti-TNF drugs are summarized in Table 1.

Do anti-TNF drugs increase the risk of serious infection?

TNF- α is a proinflammatory cytokine with a major role in RA pathogenesis. Increased levels occur systemically and at inflammation sites, and drive processes that damage cartilage and bone. TNF- α inhibition leads to significant clinical improvements and reduction of this damage [38]. This cytokine also plays a pivotal role in defense against infections, especially intracellular organisms. At the infection site,

TNF- α enhances endothelial cell activation, inflammatory cell recruitment and has a procoagulant role in limiting the spread of infection [201]. It also increases the ability of activated macrophages to phagocytose and kill mycobacteria. Infectious complications were initially considered a possible side effect of TNF- α antagonism in early animal studies [39–41], with abrogation of TNF- α in mice leading to reactivation of latent tuberculosis and outbreak of disease [42].

RA patients have approximately twice the mortality rate of the general population [43]. Serious infection (leading to hospital admission, intravenous antibiotics or death) is a major contributor to this, with the risk estimated to be two-to-three times that of the general population [44]. In considering whether any drug raises infection risks, greater background infection rates in RA need to be considered.

The data on anti-TNF drugs have produced conflicting messages, with some studies suggesting increased infection rates, and others no difference from controls. Possible reasons for this include:

- Randomized clinical trials have advantages in the analysis of rare events where disease burden, activity and comorbidities are equally distributed among patients receiving the active drug and control or placebo. However, randomized clinical trials are usually used to test efficacy and not powered to detect adverse events, being too small and of insufficient duration to provide data on rare but serious long-term hazards. In addition, randomized

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Table 1. Anti-TNF related major adverse events.

Effects	Key points	Ref.
Infection	See text	
Malignancy	See text	
Injection site reactions and infusion reactions	Injection site reactions are common (20–40%) with both etanercept and adalimumab. Usually managed with steroids and antihistamine, occasionally requiring a change of anti-TNF agent. Infliximab is associated with infusion reactions (approximately 10% – usually mild).	[1,2]
Autoimmune diseases: Lupus-like syndromes and vasculitis	Development of autoantibodies such as anti-dsDNA is common, though lupus and vasculitis is rare.	[3–8]
Congestive heart failure	Infliximab at 10 mg/kg associated with worsening CCF and mortality. Cautions advised in using the drugs in heart failure, although some studies suggest that impact on heart failure may be minimal.	[1,3,5, 9–12]
Pancytopenia, aplastic anemia neutropenia, thrombocytopenia	Occasional case reports of severe cytopenias, with largely asymptomatic neutropenia in some series.	[10, 13–17]
Demyelinating disease, optic neuritis, Guillain-Barré syndrome	Rare cases of severe demyelination and other severe neurological complications Guidelines advise to avoid if history of demyelination.	[5,10, 18–25,26]
Pulmonary fibrosis and other severe adverse lung reactions	Reports of new onset severe lung disease, or exacerbations of pre-existing disease.	[27–30]
Psoriasis	Reports of new onset of psoriasis or exacerbation of existing disease.	[31–34]
Venous thrombosis	Few reports of development of venous thrombosis following infliximab treatment.	[35–37]

clinical trials are typically conducted in lower risk patients where inclusion criteria may not make them representative of many patients treated in clinics. Infrequent adverse events are more likely to be identified by large observational databases with patients followed-up for prolonged periods;

- Anti-TNF drugs are used in patients with more severe disease, and it is difficult to separate the infection risk because of anti-TNF from the well-recognized increased risk due to RA severity [44];
- Anti-TNF agents are often given concomitantly with methotrexate and prednisolone, or other DMARDs, which may increase infection risk. Whilst data on methotrexate are reassuring [45,46], even low doses of prednisolone raise concerns. Wolfe *et al.* [45] reviewed the national databank for rheumatic diseases in the USA. They followed over 16,000 patients for 3.5 years and found the risk of hospitalized pneumonia to be 1.7-times higher in those receiving corticosteroids. Even prednisolone at doses up to 5 mg/day gave a hazard ratio of 1.4 (95% CI: 1.1–1.6).

Because of differences in results from randomized clinical trials and observational databases, this review divides studies by different methods of data acquisition.

Serious infections: randomized clinical trial data

For an increased risk

In the ASPIRE trial, 1049 patients randomized into three groups were followed for 54 weeks. Those receiving infliximab with methotrexate were more likely to experience serious infections, mainly pneumonia, than those receiving methotrexate alone [47]. Similarly, in the PREMIER trial (n = 799) of adalimumab, an increased risk of serious infections was found in those treated with adalimumab and methotrexate combined compared with either drug alone [48]. Both studies suggested a twofold increase in risk of serious infections with biologic treatment when combined with methotrexate.

A meta-analysis of nine randomized trials by Bongartz *et al.* examined the risk of serious infections in nearly 3500 RA patients receiving anti-TNF monoclonal antibody (infliximab or adalimumab) [49]. They found a doubling of risk of serious nongranulomatous infections (OR: 2.0 [95% CI: 1.3–3.1]) among users of anti-TNF agents [49]. As serious infections were based on hospitalization and intravenous antibiotic use, thresholds for these interventions would have been different between trials or arms within trials. They did not ascertain the exposure time on anti-TNF therapies, but calculated ORs assuming equality of follow-up between participants randomized to different arms in each trial.

It has been suggested that a greater dropout rate in the control arms than TNF-blocker arm (due to lack of efficacy) hinders subsequent ascertainment of events, and may underestimate the infection rate in this group. Consequently, concerns have been expressed over the conclusions of this meta-analysis [50].

Against an increased risk

Two recent short-term trials have failed to identify an increased risk of infection with anti-TNF. The START study by Westhovens *et al.* [51] showed no significant increased risk of serious infections in patients given 3 mg/kg infliximab (n = 363) compared with placebo (n = 363) at 22 weeks. However, an increased risk of serious infections was noted in patients receiving the unapproved higher dosage of 10 mg/kg with a relative risk of 3.1 when compared with placebo (95% CI: 1.2–7.9; p = 0.013). Weisman *et al.* carried out a 16-week randomized controlled trial of 535 RA patients (etanercept 266, and placebo 269), and observed no increase in the prevalence of infections (3.7% placebo and 3% etanercept) either in the total study population, or in subgroups of patients over 65 years of age, diabetics, or patients with chronic pulmonary disease [52].

Serious infections: observational data

For an increased risk

Patients enrolled onto the German biologics register (RABBIT; etanercept n = 512, infliximab n = 346, DMARD control n = 601) have been studied, and the relative risk of serious infections was 2.2 (95% CI: 0.9–5.4) for etanercept (64/1000 patient-years) and 2.1 (0.8–5.5) for infliximab (62/1000 patient-years) compared to patients on DMARDs only (23/1000 patient-years) [53]. Although the lower confidence intervals overlap with 1.0, the authors interpret these results as an increased risk of serious infection. This was independent of RA severity or duration, rheumatoid factor seropositivity, concomitant steroid use, diabetes or lung disease.

A retrospective US study by Curtis *et al.* [54] studied 3894 person-years of anti-TNF therapy and 4846 person-years of methotrexate over a median of 17 months. They demonstrated an adjusted risk of hospitalization due to bacterial infection which was 1.9-fold higher in the anti-TNF patients (4.2-fold higher in the first 6 months). The Spanish registry showed a 1.6-fold increase in rate of serious infection of 2868 patient-years on anti-TNF drugs compared

with 2433 patient-years of controls [55]. Bernat-sky *et al.* carried out a case-control cohort study of 23,733 RA patients suggesting a twofold increase in risk of all infections in patients on TNF blockers (infliximab and etanercept) [56]. However, the confidence interval was wide due to limited number of patients on anti-TNF (n = 261). Salliot *et al.* in a retrospective study of 709 RA patients found the incidence of serious infections prior to anti-TNF was 3.4 per 100 patient-years, and 10.5 afterwards [57].

Against an increased risk

In the British Register for Biologic Therapies (BSRBR), no increase in serious infections in total was found in patients treated with anti-TNF therapies compared with conventional DMARDs [58]. This was a national prospective observational study of 7664 anti-TNF and 1354 DMARD-treated RA patients. The incidence of serious infections in the anti-TNF group was 53.2 per 1000 person-years versus 41.2 in the control group. However, the frequency of serious skin and soft-tissue infections was increased in anti-TNF-treated patients (incidence risk ratio of 4.2). A total of 19 serious bacterial intracellular infections occurred, all in patients in the anti-TNF-treated cohort. Furthermore, after extended analysis, Dixon *et al.* have found an increased adjusted incidence rate of serious infection (ratio 4.6; 95% CI: 1.8–11.9) over the first 90 days after starting on anti-TNF drugs compared with DMARD therapy [59].

Klareskog *et al.* followed 686 patients for 52 weeks, and found no difference in the prevalence of serious infections in those receiving methotrexate and etanercept in combination versus either drug alone (about 4% for all groups) [60]. In a large cohort of 16,788 patients followed-up over 3.5 years, Wolfe *et al.* [45] found no increase in the pneumonia risk for anti-TNF treatment. Schneeweiss *et al.* performed a retrospective study of patients over 65 years of age, with 1900 patients on methotrexate compared with 469 on anti-TNF drugs, followed up for 0.2–1.3 years [61]. They found no increase in rate of infection in the anti-TNF group.

Tuberculous infections

Less controversial than a predisposition to infection in general is the association between anti-TNF and tuberculosis (TB) infection. TNF- α plays an important role in TB pathogenesis and in particular granuloma formation, containment and clearance of TB infection [62]. During

randomized clinical trials of anti-TNF therapy, the number of TB infections was very low. After approval of the drugs, post-marketing surveillance registers demonstrated a significant relationship between anti-TNF treatment and TB. Interpretation of the increased risk of TB requires data of the underlying risk among patients from the same location (Table 2). Some studies have focussed on differences in risk of TB between the three anti-TNF drugs. In the BSRBR, there were ten cases of TB infections [58]. The crude incidence rates for TB were 1.5, 0.9 and 0.5 events per 1000 person-years with infliximab, adalimumab and etanercept, respectively. Compared with etanercept, the adjusted incidence rate ratios (IRRs) for TB were 4.9 and 3.5 for infliximab and adalimumab, respectively. Other studies have suggested that infliximab does appear to be more predisposing to TB infection compared with etanercept (Table 2) [63–65]. This may be due to different kinetics and mechanisms of action by which the agents block TNF [66].

Most cases of TB occurred within the first 6 months of anti-TNF therapy and more often present as disseminated, extrapulmonary or atypical mycobacteria compared with the rest of the population. The overwhelming majority have occurred in patients with a known history of TB, suggesting reactivation of latent TB [66]. Risk of developing TB can be minimized by screening for previous exposure and latent TB prior to commencing anti-TNF therapy. Effectiveness of screening was shown in the Spanish register [72]. After introduction of screening recommendations and management of latent TB, the rates for active TB in biologics patients decreased by 78%. Conversely, failing to follow

recommendations is associated with a sevenfold increase in the risk of latent infection reactivation [73]. Recommendations vary between countries for TB screening because of different underlying incidence rates, and vaccination prevalences that influence risk of latent TB, and interpretation of screening test results. However, there are notable recurrent themes in recommendations:

- All patients should be screened for latent TB in accordance with national guidelines prior to starting anti-TNF therapy. Chest x-rays are universally recommended;
- Many guidelines recommend skin testing [74], whilst others suggest that immunosuppressives decrease the value of this [75]. More sophisticated and reliable tests for latent TB are becoming available, and may be incorporated into future guidelines [76];
- Patients with latent TB or at high risk of TB should receive prophylactic anti-TB treatment prior to commencing anti-TNF therapy;
- All patients on anti-TNF therapy should be closely monitored for TB.

Other opportunistic infections
Several case reports describe an association between TNF- α -inhibiting treatment and the development of opportunistic infections, but reports are few [77–81].

Wallis *et al.* examined data collected by the Adverse Event Reporting System (AERS) of the US FDA. Between January 1998 and September 2002 they found 323 cases of granulomatous infections in patients treated with infliximab or etanercept from the USA: 138 with tuberculosis, 40 with histoplasmosis, 18 with listeriosis and

Table 2. Summary of the increased risk of TB with infliximab and etanercept compared with background and rheumatoid arthritis population risks.

Country	General population	TB incidence rate (per 100,000 people) with rheumatoid arthritis			Ref.
		Without anti-TNF	With infliximab	With etanercept	
USA	6.4	6.2	61.9	NA	[64]
USA	6.4	NA	144	35	[67]
Spain	21	95	1893*	0	[68]
	21	95	1113†	0	[68]
Sweden	10	20	145	80	[69]
Korea	67.2	257	2558	0	[70]
Japan	24.8	42.4	325	NA	[71]

*2000 pre-TB screening.
†2001 post-TB screening.
NA: Not available.

Table 3. Case series of opportunistic infections.

Infection	Key points	Ref.
<i>Histoplasma capsulatum</i>	Most endemic mycosis in the USA. Second commonest pathogen to be associated with anti TNF. Disseminate in immunosuppressed patients. Inadequate data to support primary prophylaxis.	[62,67]
<i>Coccidioides immitis</i>	Endemic in USA, Mexico, Central and South America. Presents with pneumonia but risk of disseminated disease in immunosuppressed patients. Resolves with antifungal medication. Inadequate data to support primary prophylaxis.	[62,82]
<i>Listeria monocytogenes</i>	Causes sepsis in pregnant women, neonates and immunocompromised individuals. RA patients on anti-TNF should be advised to avoid high-risk foods (contaminated meats and dairy products).	[58,78,83]
<i>Pneumocystis</i> spp.	Ubiquitous. 84 reported cases of <i>Pneumocystis carinii</i> pneumonia with infliximab (some patients with Crohn's disease, but the majority of these patients were also on other immunosuppressants). Inadequate data to support primary prophylaxis.	[84,202]
<i>Cryptococcus neoformans</i>	Ubiquitous. Associated with pneumonia and meningitis. Inadequate data to support primary prophylaxis.	[85,86]
<i>Legionella pneumophila</i>	French registry search described eight RA cases, mostly on concomitant steroids and methotrexate. Relative risk calculated to be between 16.5 and 21.0 compared with normal population.	[87]

127 with other granulomatous infections [67]. Other published case series of opportunistic infections are summarized in Table 3.

Conclusions on anti-TNF & serious infections

Although the data are contradictory, it is best to exercise caution and believe that anti-TNF therapy is associated with a doubling of the increased risk of serious infection, and to approach patients with this philosophy. Recommendations can be much more definitive about the well-accepted risk of tuberculosis and other granulomatous and intracellular infections with anti-TNF therapy, where appropriate screening and ongoing vigilance is required.

Do anti-TNF drugs increase the risk of malignancies?

Overall cancer rates

TNF- α plays an important role in surveillance of malignancy [88] and hence there is a theoretical risk of increased tumor formation with anti-TNF- α agents. As with infections, data on the overall occurrence of cancer following treatment with anti-TNF- α blockers are contradictory. In summary, analyses of some randomized clinical trials raise the possibility of an increase in the occurrence of cancer. By contrast, observational studies have typically not detected an increased overall cancer risk, although excess risks of certain tumors are reported.

Already referred to above, the Bongartz *et al.* meta-analysis also raised concerns about a three-fold increased rate of malignancy with infliximab and adalimumab (OR: 3.3; 95% CI: 1.2–9.1) [49]. Moreover, the risks appear to be dose dependent, with those on high-dose therapy (defined as ≥ 6 mg/kg infliximab every 8 weeks or ≥ 40 mg adalimumab every other week) having the greatest risk (OR: 4.3; 95% CI: 1.6–11.8), with no important increased risk below these doses. Concerns on the methodology were discussed above [50]. All nine clinical trials included in this meta-analysis excluded patients with pre-existing malignancies. In addition, there was an unexpectedly low malignancy rate in the control arms when compared with the general population for this age group, which might artificially raise the comparative rates for the anti-TNF intervention arms. Four out of the nine trials included had a higher drop-out rate in their control arms, leading to less follow-up and less opportunity to develop tumors. This could lead to bias towards detection of malignancy in the anti-TNF arms during the later periods of follow-up [50].

Other studies have given reassurance that biases in this meta-analysis might inflate cancer risk. Setoguchi *et al.* describe a retrospective cohort study on two US Medicare databases and controls, which included 1152 RA patients treated with biologic therapies and 7306 treated with methotrexate [89]. There was no increased

risk of overall cancers, with a pooled adjusted hazard ratio for biologic users of 0.99 (95% CI: 0.71–1.36). Analysis of a Swedish registry by Geborek *et al.* [90] revealed no increase in the overall cancer risk (standardized incidence ratios [SIRs]: 1.1; 95% CI: 0.6–1.8) in patients receiving anti-TNF therapy compared with those that are not. Another Swedish group using a different registry have shown similar results (adjusted relative risk of 0.93 [0.76–1.13]) [91]. Results from Spanish registries [55] actually showed the rate of cancer events to be significantly higher (relative risk [RR]: 2.9) in RA patients not on anti-TNF (n = 789) compared with RA patients treated with TNF blockers (n = 4459).

In support of above studies, the most recent data from a large US observational study concluded that biologics use in RA was not associated with increased overall risk of any malignancy [92]. However, when examined separately, the risks for both nonmelanotic skin cancer and melanoma were increased with biologic therapy (OR: 1.5; 95% CI: 1.2–1.8; OR: 2.3; 95% CI 0.9–5.4, respectively). Similarly, data from a large cohort study by Chakravarty *et al.* [93] showed an increased risk for developing nonmelanoma skin cancer (NMSC) in RA patients treated with anti-TNF agents (hazard ratio: 1.19, $p = 0.042$). In the meta-analysis of Bongartz *et al.*, many malignancies in the anti-TNF arms of the trials were NMSC (nine out of 35) [49]. The Swedish Biologic Register signals a possible increased occurrence of NMSC in RA cohort treated with anti-TNF (RR: 1.55; 95% CI: 0.76–3.15, $n = 10$) [91].

In screening patients prior to undergoing anti-TNF therapies, caution needs to be exercised where there is a history of previous malignancy. Watson *et al.* compared a group of 154 patients with RA and previous cancer with a group of 9844 patients with RA but no previous malignancy. Six patients (4%) who had previous malignancy developed a new cancer, compared with 158 patients (1.6%) without previous malignancy (IRR: 2.5 [95% CI: 1.2–5.8]) [94]. These data are yet to be fully published, but ongoing caution in these patients is required.

Lymphoma

Patients with RA not exposed to anti-TNF drugs have an increased incidence of lymphoma (particularly non-Hodgkins lymphoma), ranging from two- to 25-fold. The risk appears to be particularly elevated in patients with sustained high levels of disease activity [95–97]. It is unclear

to what extent this increased risk is from the disease alone or related therapies, especially with azathioprine and methotrexate [98,99].

Safety concerns regarding anti-TNF- α blockers and lymphoma arose after the US FDA's postmarketing spontaneous adverse event reporting system (MedWatch) received reports of lymphoma. Brown *et al.* reviewed MedWatch reports of 26 cases of lymphoproliferative disorders that occurred following treatment with etanercept or infliximab [100]. Of the lymphomas, 54% were detected within 8 weeks of anti-TNF treatment initiation, and two patients remitted after cessation of treatment. Subsequent studies showing support for and against an increased risk of lymphoma in RA patients are summarized in Table 4. The studies of Wolfe and colleagues are informative. When the original study covering 29,314 patient-years [101] was extended to 89,710 patient-years [102], the originally described increase in lymphomas associated with anti-TNF therapy disappeared. In the second study, not only were more data available, but the authors carefully controlled for disease severity. This illustrates the need for long-term data and, in observational databases, controlling for differences in the populations that are studied.

Conclusions on anti-TNF & malignancies

Despite theoretical concerns about predisposition to cancer with anti-TNF therapies, no consistent signal for concern has emerged to date from randomized clinical trials or observational databases. However, development of skin tumors should be monitored closely, and ongoing scrutiny of observational databases will be needed to make sure that long-term suppression of TNF- α is not associated with late-tumor development. Patients with previous cancer have to be monitored closely because of the possibility that they might be more vulnerable to subsequent tumor development on anti-TNF drugs.

Future perspective

- Regular updates of long-term observational databases are needed to guard against complacency on serious side effects;
- Better tests for screening for latent tuberculosis and other opportunistic infections will be incorporated into guidelines and clinical practice;
- Patients at heightened risk of malignancy will be better identified.

Table 4. Studies demonstrating evidence for and against an increased risk of lymphoma associated with anti-TNF therapy.

Country	Number of patients	Study type	Key points	Ref.
Against an increased risk				
USA/Canada	1152 biologic users versus 7306 MTX users	Retrospective cohort study	Infliximab, etanercept and adalimumab. Pooled hazard ratio for hematologic malignancy comparing with MTX user is 1.37 (95% CI: 0.71–2.65).	[89]
Sweden	4160 biologic users versus 53,067 RA cohort (inpatient registry)	Observational	Infliximab, etanercept and adalimumab. SIR of lymphoma in RA cohort was 1.9 versus 2.9 in biologic user. No significant increased risk compared with control – RR of 1.1 (0.6–2.1).	[103]
USA	10,775 biologic user versus 8816 DMARD user	Observational	Infliximab, etanercept and adalimumab Odds ratio of 1.0 when compared with control (95% CI: 0.6–1.8).	[102]
For an increased risk				
USA	18,572 RA patients, 8614 on biologics	Observational	Infliximab, etanercept and anakinra. Standard incidence ratio for lymphoma in patients treated with biologics was 2.9 (95% CI: 1.7–4.9). Did not adjust for baseline differences in disease duration and severity.	[101]
Sweden	757 biologic users versus 800 DMARD users	Retrospective cohort study	Infliximab and etanercept. SIR for lymphoma was 11.5 (95% CI: 3.7–26.9) and 1.3 (95% CI: 0.2–4.5) for controls. Fivefold increase of lymphoma incidence among RA patients exposed to anti TNF agents. Possibility of confounding by indication and low rate of lymphoma in control population.	[90]
Meta-analysis	3493 TNF users versus 1512 RA controls	Data from nine randomized clinical trials	Infliximab and adalimumab. Identified ten lymphomas cases in anti-TNF treated patients compared with no lymphomas in non-anti-TNF-treated patients.	[49]

CI: Confidence interval; DMARD: Disease-modifying antirheumatic drug; MTX: Methotrexate; RA: Rheumatoid arthritis; RR: Relative risk; SIR: Standardized incidence ratio.

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Executive summary

Do anti-TNF drugs increase the risk of serious infection?

- Although there is not a strong consensus, a doubling of risk of serious infections with anti-TNF therapy should be accepted.
- Tuberculosis is undoubtedly a cause for concern, and needs to be screened for prior to therapy, and monitored closely for emergence thereafter. In endemic areas other granulomatous and intracellular organisms may need to be considered.
- All patients need to be counseled about the risks of anti-TNF therapy, including risk of serious infections as well as the benefits many patients experience.

Do anti-TNF drugs increase the risk of malignancy?

- The data are contradictory, with some studies showing an increased risk, and others not.
- There are concerns over skin cancers and possible heightened risks for patients with previous tumors.

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