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FACULTAD DE MEDICINA Y CIENCIAS BIOMÉDICAS
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HOSPITAL CENTRAL DEL ESTADO DE CHIHUAHUA



**USO DE ESCALA CARG EN PREDICCIÓN DE QUIMIOTOXICIDAD EN
ADULTO MAYOR CON CÁNCER HEMATOLÓGICO ATENDIDOS EN EL
CENTRO DE CANCEROLOGÍA DE CHIHUAHUA EN EL PERIODO DE 2020 A
2023.**

**PRESENTA:
ELOY GARZA RAMOS**

**TESIS PRESENTADA COMO REQUISITO PARA OBTENER EL GRADO DE
ESPECIALIDAD EN GERIATRIA**

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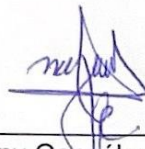
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P R E S E N T E.-

La que suscribe, Jefa de Enseñanza Médica del Hospital Central del Estado.

HACE CONSTAR

Que el DR. ELOY GARZA RAMOS, residente de la especialidad de **GERIATRIA** de Cuarto Año, entregó en forma su tesis:

“USO DE ESCALA CARG EN PREDICCIÓN DE QUIMIOTOXICIDAD EN ADULTO MAYOR CON CÁNCER HEMATOLÓGICO ATENDIDOS EN EL CENTRO DE CANCEROLOGÍA DE CHIHUAHUA EN EL PERIODO DE 2020 A 2023”

Así mismo manifiesto que no tiene adeudo alguno en este Hospital, y después de valorar su caso en el comité de investigación del Hospital se autoriza liberación de su tesis para continuar con sus trámites.

Se expide la presente a petición del interesado para los fines que le convengan, en la ciudad de Chihuahua, Chih. a los 09 días del mes de MAYO del 2024.



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RESUMEN

USO DE ESCALA CARG EN PREDICCIÓN DE QUIMIOTOXICIDAD EN ADULTO MAYOR CON CÁNCER HEMATOLÓGICO ATENDIDOS EN EL CENTRO DE CANCEROLOGÍA DE CHIHUAHUA EN EL PERIODO DE 2020 A 2023.

Introducción: El envejecimiento de la población mexicana presenta un desafío importante para el sistema de salud, ya que aumenta la prevalencia de enfermedades crónicas como el cáncer. Las enfermedades hematológicas malignas, como la leucemia, el linfoma y el mieloma múltiple, son más comunes en las personas mayores.

Objetivo: Del periodo del 2020 a 2023, en el centro estatal de cancerología de chihuahua, se implementó la escala GARG para la determinación de riesgo de quimiotoxicidad en cáncer hematológico, así como, el porcentaje de éxito en la detección de esta.

Material y Métodos: Se realizó un estudio con 42 pacientes y se aplicó la escala CARG para evaluar su estado funcional. Se comparó la precisión de la escala CARG con las herramientas comúnmente utilizadas en oncología para predecir la toxicidad.

Resultados: La escala CARG mostró una sensibilidad del 95%, una especificidad del 60%, un valor predictivo positivo del 72.41% y un valor predictivo negativo del 92.30%. Se encontró una asociación significativa entre la estadificación de riesgo según la escala CARG y la incidencia de toxicidad.

Conclusión: La escala CARG es una herramienta superior a las utilizadas actualmente para predecir la toxicidad de la quimioterapia en pacientes de edad avanzada con enfermedades hematológicas malignas. Su uso podría ayudar a reducir el tiempo de internación hospitalaria, los costos y mejorar la toma de decisiones médicas, optimizando el uso de la quimioterapia.

Palabras clave: Cáncer hematológico, Envejecimiento de la población, Enfermedades hematológicas malignas, Herramienta de predicción, Toxicidad.

ABSTRACT

USE OF THE CARG SCALE IN PREDICTING CHEMOTHERAPY TOXICITY IN ELDERLY PATIENTS WITH HEMATOLOGICAL CANCER TREATED AT THE CHIHUAHUA CANCER CENTER FROM 2020 TO 2023

Introduction: The aging of the Mexican population presents a significant challenge to the healthcare system, as it increases the prevalence of chronic diseases such as cancer. Hematological malignancies, such as leukemia, lymphoma, and multiple myeloma, are more common in older adults.

Objective: From 2020 to 2023, the GARG scale was implemented at the Chihuahua State Cancer Center to determine the risk of chemotherapy toxicity in hematological cancer, as well as the percentage of success in detecting it.

Materials and Methods: A study was conducted with 42 patients and the CARG scale was applied to evaluate their functional status. The accuracy of the CARG scale was compared with commonly used tools in oncology to predict toxicity.

Results: The CARG scale showed a sensitivity of 95%, a specificity of 60%, a positive predictive value of 72.41%, and a negative predictive value of 92.30%. A significant association was found between the risk staging according to the CARG scale and the incidence of toxicity.

Conclusion: The CARG scale is a superior tool to those currently used to predict chemotherapy toxicity in elderly patients with hematological malignancies. Its use could help reduce hospital length of stay, costs, and improve medical decision-making, optimizing the use of chemotherapy.

Keywords: Hematological cancer, Aging population, Hematological malignancies, Prediction tool, Toxicity.

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1. MARCO TEÓRICO

México enfrenta un reto inmediato para su sistema de salud, el envejecimiento poblacional, por primera vez los individuos mayores de 60 años superan a los menores de 5 años.

Los adultos mayores son el grupo de edad que más utiliza los servicios médicos y de entre las diferentes enfermedades, el manejo de cáncer en el paciente geriátrico es un contexto delicado y preocupante entre los médicos oncólogos.

Conseguir un método práctico y eficaz para el médico oncólogo previo a la valoración de geriatría es de vital importancia, ante el desafío de mantener su práctica médica en el centro de una revolución demográfica como resultado del envejecimiento universal de la población principalmente en occidente y la falta de profesionales en geriatría, los médicos oncólogos requerirán herramientas para toma de decisiones rápidas durante su ejercicio médico.

El factor individual más importante en contexto de enfermedad neoplásica es el envejecimiento, más del 60 % de los casos de cáncer en Estados Unidos de América ocurre en los mayores de 65 años.

Del total de la población mexicana se estima que en 2050 los mayores de 60 años representaran el 21.5 % de la población, con una esperanza de vida de 80 años.

La edad media del diagnóstico de todos los cánceres combinados es de 69 años para el varón y 67 años para la mujer, con un ajuste de incidencia por edad 10 veces mayor en los adultos mayores de 65 años.

Los avances en las ciencias biomédicas así como las mejores de las condiciones de vida han desencadenado una disminución en la morbilidad y mortalidad de enfermedades transmisibles, caso contrario a las enfermedades crónicas no transmisibles, esto lo traducimos a una mayor longevidad de la población, lo cual de manera lógica significa una mayor carga de morbilidad, discapacidad y necesidad de cuidados, de cara a la mayor exposición de carcinógenos y acumulación de



trastornos genéticos, de manera inmediata supone un desafío al sistema de salud mexicano, donde estas necesidades no son cubiertas.

Actualmente una persona de 65 años como promedio es esperado una expectativa de vida por lo menos de 15 años y que mantuviera un nivel de independencia durante la mayor parte del tiempo. Para las personas de 75 a 85 años sería esperado un promedio de 10 y hasta 6 años de expectativa de vida respectivamente, estimando un nivel de independencia la mayor parte del tiempo.

La discapacidad y la dependencia suponen un determinante de nuevos requerimientos para los cuales se carece de una respuesta.

Es destacable que el bajo nivel de capacidad intrínseca de los individuos da lugar a un estado de vulnerabilidad.

El deterioro de las reservas fisiológicas sea por envejecimiento o por enfermedad es la principal causa de fragilidad dentro de la comunidad. Partiendo de su definición y de un modo práctico, cualquier circunstancia que cambie el riesgo de resultados adversos en las personas mayores contribuye a la fragilidad. (1)

Dicho deterioro ocurre en el contexto de estrés entre las exposiciones y la resiliencia a un ritmo individual, lo que resulta en una alta variedad de diferentes edades biológicas individuales en sujetos de edad cronológicamente similares.

Partiendo de lo anterior es innegable que la función específica de cada órgano declina a cifras diferentes en cada persona en lo individual, por lo tanto teniendo una población mayormente heterogénea refiriéndonos a expectativa de vida y estado funcional, supone un desafío para los oncólogos y geriatras; a la hora de determinar los beneficios y tolerancia al tratamiento de cáncer.

En base a esto parte la aplicación de la evaluación compresiva del paciente geriátrico, con importantes efectos positivos en adulto mayor frágil, sugerido por varios estudios observacionales su aplicación para la toma de decisiones y guía de tratamiento.



El concepto de fragilidad o síndrome de fragilidad, caracterizado por alta susceptibilidad, baja reserva funcional y homeostasis inestable, lo resumimos en un estado clínico de vulnerabilidad, dicho estado cobra importancia en oncología a fin de identificar a los pacientes en edad avanzada susceptibles al desarrollo de toxicidad y efectos secundarios graves en respuesta a tratamiento.

En los adultos mayores, el deterioro funcional se asocia con un mayor riesgo de mala supervivencia, institucionalización y hospitalización. En adultos mayores con cáncer, el estado funcional alterado a menudo se asocia con la decisión y la viabilidad del tratamiento. (34), así como un aumento de la quimiotoxicidad.

El cáncer en el adulto mayor

La oncología geriátrica une los campos de la oncología y la geriatría para efectuar un manejo interdisciplinario específico en los adultos mayores con cáncer. Con el objetivo de individualizar el tratamiento y seguimiento de los pacientes buscando maximizar los beneficios del tratamiento, controlar las comorbilidades, disminuir la toxicidad y aumentar la supervivencia. (26)

El cáncer y el envejecimiento son procesos dinámicos, interactúan e interfieren de diversas formas, la tumoración maligna sugiere una sinergia entre la acumulación de mutaciones y la edad de la persona, lo que conlleva a cambios protooncogénicos en el medio celular, todo ello concluye en un proceso proliferación y expresión de fenotipo neoplásico.

En años recientes se ha identificado marcadores moleculares de envejecimiento y riesgo a cáncer, tales como el funcionamiento de telomerasa lo cual podrá permitir una predicción para el desarrollo de cáncer, así como intervenciones terapéuticas.

El envejecimiento induce cambios en las capacidades funcionales de los órganos que deben ser considerados para la planificación y dosificación de farmacoterapias. Los cambios relacionados con la edad en las funciones de los órganos pueden afectar todos los parámetros farmacocinéticos y farmacodinámicos.



Todo lo cual contribuye a una alta variabilidad en la captación gastrointestinal de fármacos. Como la perfusión del hígado también disminuye con la edad, el metabolismo de los fármacos puede prolongarse favoreciendo una mayor toxicidad.

Mecanismos comunes del cáncer y el envejecimiento

Entre los cambios fisiológicos del envejecimiento registrados en la literatura científica encontramos la disminución de volumen cortical en el sistema nervioso central; la disminución en la absorción, metabolismo y eliminación de fármacos; la disminución del filtrado glomerular; la disminución del gasto cardiaco, así como la disminución de la capacidad vital pulmonar e intercambio de gases. (1) Adicionalmente, se han estudiado otros cambios relacionados directamente con el desarrollo de cáncer. Estos cambios no necesariamente ocurren al mismo tiempo en el mismo individuo, y difieren entre cada persona. (2,3) (tabla 1)

El deterioro fisiológico asociado al envejecimiento es el responsable del alto riesgo de toxicidad asociada a la quimioterapia en el anciano oncológico. (19) Distintos estudios indican que el riesgo de que un anciano tratado con quimioterapia presente algún tipo de evento adverso asociado al uso de fármacos es del 90,1-91,5%. (20)

Estos cambios fisiológicos relacionados al envejecimiento, y las consecuencias que pueden proceder de ellos, permiten vislumbrar un cambio en el manejo de la medicación del anciano oncológico, y por ende de la quimioterapia. La mejor manera hasta este momento para conocer una aproximación de la edad fisiológica de un paciente mayor más que su edad biológica, es la correcta implementación de la valoración geriátrica integral (VGI).

Tabla 1 Mecanismos fisiológicos comunes entre el cáncer y el envejecimiento

Mecanismos fisiológicos comunes entre el cáncer y el envejecimiento	
Mecanismos del envejecimiento	Implicaciones en cáncer
Fragilidad - Disminución de la reserva fisiológica - Mayor vulnerabilidad - Fenotipo de fragilidad • Debilidad • Actividad física reducida • Coordinación motriz lenta • Cansancio fácil • Pérdida de peso	La disminución de la reserva fisiológica predispone al adulto mayor a un estado de vulnerabilidad ante estresores externos y mayor riesgo de presentar complicaciones posquirúrgicas y mortalidad en pacientes que reciben quimioterapia
Inflamación - <i>Inflammaging</i> • Aumento de mediadores inflamatorios en ausencia de enfermedad • Contribuye significativamente al desarrollo de comorbilidades	Aumenta el riesgo de cáncer, promueve la activación de mutaciones genéticas iniciales o de mecanismos epigenéticos que conducen a carcinogénesis. En células con cáncer puede contribuir a progresión y metástasis
Inmunosenescencia - El envejecimiento es un estado de inmunosenescencia - La disfunción inmunitaria e inflamación crónica pueden promover la activación de enfermedades autoinmunes, así como la carcinogénesis	La acumulación de células senescentes contribuye al envejecimiento de células no cancerosas e induce un estado de inmunodeficiencia y por tanto puede afectar tolerancia al tratamiento

Evaluación clínica del paciente de edad avanzada

A medida que envejecemos, nuestras reservas biológicas para enfrentar el estrés disminuyen naturalmente. Esto se ve agravado por la presencia de enfermedades crónicas comunes en las personas mayores. La capacidad para responder al estrés varía de persona a persona y no siempre se refleja en la edad cronológica.

Este declive en la capacidad para enfrentar el estrés tiene un impacto significativo en la salud y el bienestar de las personas mayores. Afecta aspectos como la esperanza de vida, la capacidad funcional, la necesidad de asistencia, la tolerancia al estrés, la rehabilitación y el manejo de condiciones especiales como la depresión, la desnutrición y la polifarmacia. En conjunto, estos factores comprometen la calidad de vida y la supervivencia de las personas mayores.

Es importante destacar que los cambios relacionados con la edad no son uniformes en todas las personas. La capacidad para enfrentar el estrés varía considerablemente entre individuos, incluso aquellos de la misma edad cronológica. La comprensión de la relación entre el envejecimiento, la capacidad para enfrentar el estrés y la salud es crucial para brindar una atención médica adecuada a las personas mayores. Se necesitan enfoques individualizados que consideren las



diferentes necesidades y capacidades de cada persona para promover una mejor calidad de vida y una mayor esperanza de vida.

La valoración geriátrica integral que incluye estado funcional, condiciones médicas comórbidas, estado cognoscitivo, estado nutricional, estado psicológico, apoyo social; así como revisión de medicamento. Es el sistema que mejor toma en cuenta las diversidades del paciente para la toma de decisiones. Teniendo como ventajas:

1. Reconocimiento de condiciones en potencia tratables; depresión, desnutrición, que pueden reducir la tolerancia al tratamiento del cáncer.
2. Evaluación de reserva funcional individual.
3. Estimación de expectativa de vida del individuo.
4. Adaptación de un lenguaje común para clasificar a los pacientes.

Teniendo en cuenta los resultados de la valoración es posible descubrir problemas relevantes al tratamiento con cáncer que de otra forma pasaría inadvertidos. Numerosos estudios muestran evidencia de recuperación en estado funcional, disminución de hospitalización e impacto positivo en sobrevida, al llevar a cabo su correcta aplicación.

La valoración geriátrica integral, permite al médico reconocer al menos tres etapas del envejecimiento en lo que aplica a su vez el tratamiento oncológico:

1. Personas con funcionalidad independiente y sin comorbilidad y que son candidatos para cualquier forma de tratamiento oncológico.
2. Personas frágiles, con dependencia en una o más actividades de la vida diaria, tres o más comorbilidades, uno o más síndromes geriátricos; se les considera candidatos a tratamiento paliativo.
3. Personas intermedias, que se benefician de algún tratamiento farmacológico, tal como reducción en dosis inicial de quimioterapia con escalamiento subsecuente.

La VGI incluso permite planificar intervenciones no oncológicas, en el 26-70% de los casos (27). Actualmente, la conclusión de los médicos expertos en oncogeriatría,



es la propuesta de las intervenciones no oncológicas que se han de efectuar si se revela algún déficit en la VGI.

Se han publicado distintos modelos de VGI en ancianos oncológicos, pero no existe unanimidad en cuanto al modelo de VGI que se debe emplear (28).

Otras formas de evaluación geriátrica

La valoración geriátrica por muchos médicos puede considerarse como compleja y con la desventaja de un alto consumo de tiempo, además de que no se existe un acuerdo universal de cuál sea la forma más productiva de llevarla a cabo. Todo ello aunado a la falta de personal especializado en el área de geriatría además de la alta demanda de un especialista en oncología para realizar la toma de decisiones rápidamente durante su valoración, nos conduce a buscar formas alternativas de realizar una evaluación rápida y precisa que incluya el cuestionamiento de la actividad física y estudios de laboratorio.

Se han propuesto diversos cuestionarios de detección, con la finalidad de establecer y detectar a los pacientes con mayor riesgo de muerte, dependencia funcional, riesgo de complicaciones al tratamiento de cáncer y quiénes serían candidatos a una valoración más compleja por parte de un especialista en geriatría.

Las cuestiones más importantes para resolver respecto a la evaluación del anciano oncológico son:

- a) cuál es el grupo de pacientes que más se pueden beneficiar de una VGI, aunque la mayoría de los estudios han utilizado los 70 años como punto de corte a partir del cual aplicarla.
- b) identificar una herramienta de cribado que permita seleccionar a aquellos ancianos que más pueden beneficiarse de la VGI. (28)

Se ha investigado sobre las denominadas herramientas de cribado, que permitan hacer una selección de aquellos ancianos en los que sea necesaria aplicar la VGI evitando su aplicación a todos y cada uno de los ancianos de la consulta.



Evaluación funcional del paciente mayor con cáncer

La mayoría de los médicos continúa utilizando el KPS (Karnofsky Performance Status) o la escala ECOG (Eastern Cooperative Oncology Group), para comprobar actividades diarias básicas, dichas escalas fracasan en detección de alteraciones funcionales instrumentales, es de notar que hasta 80% de los adultos mayores con cáncer estimen ECOG de 0 a 1 al diagnóstico, siendo que más del 50 % en requieren asistencia en actividades cotidianas. (29)

Según un estudio, individuos con buen ECOG-PS (ECOG-PS<2), eran comórbidos en el 13% de los casos, presentaban deterioro cognitivo y/o emocional en el 30%, eran dependientes en ABVD (actividades básicas de la vida diaria) en el 9,3% de los casos y dependientes en AIVD (actividades instrumentales de la vida diaria) en el 37,7%. (30)

En otro estudio, el 54% de los ancianos con IK 100% y el 48% de los ancianos con IK 90% presentaban toxicidad severa de algún tipo (grados 3-5), a pesar de tener una excelente situación basal (11). Dichos estudios muestran que la situación basal del anciano, entendida solo por la información aportada por el ECOG-PS o por el IK, no es suficiente en la valoración del anciano.

En el paciente mayor, la finalidad de dicha evaluación es la identificación de los aspectos funcionales finos que contribuyen a la morbilidad además de la predicción de intolerancia al manejo farmacológico de cáncer.

Con el envejecimiento continuo de la población, se requerirá que los oncólogos hagan decisiones difíciles y complejas en cuanto al tratamiento de pacientes mayores con cáncer. La edad cronológica no es un indicador confiable sobre el estado físico y psicológico, no debe de ser el factor principal para la toma de decisiones de tratamiento. Analizar la situación global del paciente mediante una herramienta práctica multidimensional, deberá brindar destrezas y materiales para predecir los riesgos y beneficios del tratamiento personalizado para los pacientes.

Reconocer al paciente que no se beneficia de quimioterapia en dosis estándar es una tarea importante. En los adultos mayores con fragilidad la terapia a dosis



reducida es la opción que aporta mayor beneficio a su situación sin llegar a complicar su estado basal. Contar una herramienta de selección sintetizada para el reconocimiento rápido de los pacientes es indispensable en la práctica oncológica diaria.

Aspectos geriátricos en neoplasias hematológicas

Dentro del ámbito de la hematología, la leucemia representa aproximadamente el 8.5% de los casos, seguida del linfoma no Hodgkin con un 6.25%, el linfoma Hodgkin con un 2% y el mieloma múltiple con un 1.8%. (31-33)

Las enfermedades hematológicas malignas conforman un grupo heterogéneo de patologías cuya incidencia se incrementa con la edad, alcanzando su pico máximo entre los 75 y 99 años. En este grupo de edad, la supervivencia global es baja, especialmente en el caso de las leucemias agudas.

La diferencia entre la edad cronológica (edad real) y la edad biológica (estado físico real) de una persona puede ser considerable. Esto significa que basarse únicamente en la edad cronológica de un adulto mayor puede subestimar su capacidad funcional.

En el caso de las personas mayores con neoplasias hematológicas (cáncer de la sangre), su pronóstico general dependerá de su estado de salud actual, más allá de la malignidad en sí o de la fragilidad preexistente. Considerar solo estos dos últimos factores conduce a un pronóstico incompleto. (1)

La fragilidad en pacientes con cáncer de la sangre (neoplasias hematológicas malignas) puede empeorar su pronóstico de varias maneras, según estudios previos. (11-14) Entre estas consecuencias negativas más comunes encontramos, mayor probabilidad de sufrir efectos secundarios graves por el tratamiento hematológico, mayor riesgo de padecer enfermedades que no estén relacionadas con el tratamiento hematológico, necesidad de suspender o interrumpir el tratamiento hematológico debido a la fragilidad del paciente, mayor mortalidad, tanto por el cáncer de la sangre como por las complicaciones del tratamiento, en comparación con pacientes no frágiles. (1)



Las neoplasias hematológicas (NH) son un conjunto de enfermedades que se originan por la multiplicación descontrolada de células sanguíneas (células hematopoyéticas). Estas células sufren alteraciones en su proceso de maduración, adquiriendo características propias de la enfermedad.

Las neoplasias hematológicas tienen como característica estar diseminadas por todo el cuerpo al momento del diagnóstico, afectando principalmente la médula ósea, el lugar donde se producen las células sanguíneas. Debido a las peculiaridades de estas células, las neoplasias hematológicas son sensibles a tratamientos como la radioterapia y la quimioterapia. (4)

Las estrategias de tratamiento para las neoplasias malignas hematológicas varían según el tipo de cáncer:

- Leucemia mieloide aguda: Se emplea quimioterapia intensiva con el objetivo de curar la enfermedad, o se opta por un tratamiento farmacológico no curativo si la cura no es posible.
- Mieloma múltiple: Se puede aplicar quimioterapia de alta dosis con trasplante autólogo de células madre, o se pueden considerar manejos sin trasplante según las características del paciente.
- Linfoma difuso de células B grandes: El objetivo es la quimioinmunoterapia curativa para lograr la remisión completa de la enfermedad. En caso de no ser posible, se utiliza quimioterapia paliativa para controlar la enfermedad y mejorar la calidad de vida del paciente.
- Cáncer de la sangre en recaída o refractario: El trasplante alogénico de células madre hematopoyéticas se considera como última opción de tratamiento en estos casos.

En una revisión sistemática entre personas mayores con neoplasias hematológicas en las que los médicos detectaron un buen estado funcional, se encontró que numerosas personas tenían características asociadas con la fragilidad tales como, la polifarmacia (es decir la ingesta de al menos cinco medicamentos) o deterioro cognitivo, trastornos emocionales, problemas nutricionales y deterioro de la capacidad física o actividades de la vida diaria. (1)



Estos padecimientos pueden presentar pancitopenia secundaria a la enfermedad y posteriormente relacionada con tratamiento condicionando hemorragia e infecciones, lo cual junto con las comorbilidades preexistentes reducen las probabilidades de remisión y en el pronóstico de vida. (4)

Leucemias en el adulto mayor

De manera general son enfermedades malignas originadas en la medula ósea. El tipo celular de origen tanto linfocitario como mieloide. Existen cuatro tipos principales de interés;

1. Leucemia linfoblástica aguda (LLA)
2. Leucemia mieloide aguda (LMA)
3. Leucemia linfocítica crónica (LLC)
4. Leucemia mieloide crónica (LMC)

Aunque los manejos médicos han mejorado en décadas recientes, la tasa de respuesta favorable del adulto mayor se mantiene en bajas por múltiples razones, incluyendo cambios biológicos, comorbilidades y deterioro en funcionalidad. Lo cual condiciona a peor tolerancia al tratamiento. Debido al envejecimiento poblacional se espera un aumento a 68% en 2030 en EUA.

Leucemia linfoblástica aguda

La incidencia de la Leucemia Linfoblástica Aguda (LLA) aumenta con la edad. Un número significativo de pacientes con LLA, aproximadamente el 20%, son mayores de 55 años al momento del diagnóstico, y esta cifra aumenta al 12% para los mayores de 65 años. Un factor que complica el tratamiento de la LLA en adultos mayores es la necesidad de quimioterapia intensiva, la cual puede ser menos tolerada debido a los cambios fisiológicos asociados con el envejecimiento.

Lograr la remisión completa (ausencia de células leucémicas) es crucial para la supervivencia a largo plazo en la Leucemia Linfoblástica Aguda (LLA). La fase de



inducción del tratamiento, la cual busca eliminar la mayor cantidad de células leucémicas posible, es particularmente crítica en adultos mayores. Lamentablemente, esta población presenta una tasa de mortalidad de hasta el 42% durante esta etapa, incluyendo casos de muerte temprana al inicio de la quimioterapia.

En países desarrollados, las tasas de supervivencia global para la Leucemia Linfoblástica Aguda (LLA) son bajas, oscilando entre el 12% y el 25%. En el caso de los adultos mayores, la principal modificación al tratamiento estándar ha sido la eliminación de la asparaginasa y la reducción de la dosis de antraciclinas, debido a que hasta el 30% de estos pacientes presentan un estado funcional deficiente al momento del diagnóstico, lo que los hace candidatos a cuidados paliativos.

Sin embargo, el uso de inhibidores de tirosina cinasa (ITC) ofrece una alternativa prometedora para adultos mayores con LLA y cromosoma Filadelfia positivo (Ph+). Estos medicamentos han demostrado lograr tasas de remisión más altas que en pacientes Ph-negativo. Además, existe evidencia que sugiere que la combinación de ITC con dosis reducidas de quimioterapia puede inducir remisión con baja mortalidad en adultos mayores.

Actualmente el desarrollo de nuevos agentes como el uso específico de anticuerpos es prometedor especialmente por mínimos efectos mielosupresores.

Leucemia Mieloide Aguda

La leucemia mieloide aguda (LMA) es un tipo de cáncer de la sangre que se caracteriza por la proliferación anormal de células progenitoras mieloides en la médula ósea, la sangre y otros tejidos. Esta proliferación descontrolada da lugar a una disminución en el número de células sanguíneas normales (citopenias).

Siendo la segunda leucemia más común en adultos, la LMA se diagnostica en promedio a los 67 años, y cerca de un tercio de los pacientes tienen más de 75 años. El riesgo de desarrollar LMA aumenta con la edad, y la supervivencia global



a los cinco años es de solo un 5%, con opciones de tratamiento limitadas para los adultos mayores.

Un factor que contribuye al aumento de la incidencia de LMA en adultos mayores es el desarrollo de LMA secundaria a síndromes mielodisplásicos (SMD) u otras neoplasias hematológicas.

El pronóstico de la leucemia mieloide aguda (LMA) en adultos mayores es desalentador debido a la resistencia de las células leucémicas al tratamiento con quimioterapia, causada por mutaciones genéticas, y a las características propias del paciente. La causa exacta de la LMA aún se desconoce, pero se cree que el riesgo de desarrollarla está asociado a factores ambientales, predisposición genética e inmunosenescencia (debilitamiento del sistema inmunológico asociado a la edad).

En el adulto mayor, la fatiga es el síntoma más común de la LMA, afectando a más del 90% de los pacientes. Esto tiene un impacto significativo en la calidad de vida, ya que hasta el 97% de los pacientes mayores de 60 años con LMA priorizan la calidad de vida por sobre la duración de la enfermedad.

En pacientes frágiles o con enfermedad de mal pronóstico, la quimioterapia intensiva no ofrece ningún beneficio. De hecho, las terapias de baja intensidad, como la citarabina, combinadas con cuidados paliativos, resultan ser más beneficiosas para este grupo de pacientes. Por otro lado, los pacientes con buen estado de salud y riesgo citogenético favorable son candidatos a terapia de inducción.

Leucemia Linfocítica Crónica

La leucemia linfocítica crónica (LLC) es el tipo de leucemia más comúnmente diagnosticado, con una incidencia de 4.2 casos por cada 100,000 habitantes. Se considera una enfermedad del adulto mayor, ya que el 70% de los pacientes tienen más de 65 años. El único factor de riesgo claramente identificado es la historia familiar, con un riesgo 2.5 veces mayor para los familiares de pacientes con LLC.



El curso clínico de la LLC es variable, y muchos pacientes no requieren tratamiento durante varios años. La elección del tratamiento depende de la tolerancia del paciente a la quimioterapia, considerando factores como la edad, el estado físico y la depuración de creatinina.

Leucemia Mieloide Crónica

La Leucemia Mieloide Crónica (LMC) es un tipo de cáncer que se origina en las células madre de la sangre. Esta enfermedad se produce por un intercambio anormal entre los cromosomas 9 y 22, lo que genera un cromosoma anómalo llamado cromosoma Filadelfia. Este cromosoma produce un gen que estimula la proliferación y la inestabilidad genética de las células leucémicas.

La LMC presenta un curso clínico en tres fases: crónica, acelerada y blástica. La mayoría de los pacientes (80%) son diagnosticados en la fase crónica.

Linfoma no Hodgkin

Los linfomas no Hodgkin (LNH) son un conjunto de enfermedades cancerosas que afectan al tejido linfóide, el cual forma parte del sistema inmunológico. A nivel mundial, el linfoma no Hodgkin es el octavo tipo de cáncer más común en hombres, tanto en términos de incidencia como de mortalidad, según datos de GLOBOCAN 2012. (21)

Los linfomas no Hodgkin (LNH) se dividen en más de 20 subtipos distintos, los cuales se diferencian por sus características morfológicas, citogenéticas e inmunofenotípicas. (24)

El comportamiento del linfoma no Hodgkin (LNH) varía según el subtipo histológico. Los linfomas de bajo grado son de crecimiento lento y pueden entrar en remisión sin necesidad de tratamientos intensivos, mientras que los linfomas de alto grado son más agresivos y se desarrollan con mayor rapidez. (23)

La edad juega un papel crucial en el pronóstico del linfoma no Hodgkin (LNH). En los pacientes de edad avanzada, la capacidad de tolerar los tratamientos se ve limitada por la disminución de la función de varios órganos, la presencia de más



enfermedades comórbidas y la mayor resistencia de la enfermedad a la quimioterapia.

Mieloma Múltiple

El mieloma múltiple, un cáncer de las células plasmáticas, tiene una incidencia global del 0,8% (GLOBOCAN 2012) y se diagnostica principalmente en personas de alrededor de 70 años. Debido a la edad y a otras enfermedades coexistentes (comorbilidades), los pacientes con mieloma múltiple tienen un mayor riesgo de sufrir complicaciones de salud.

El daño orgánico causado por el mieloma múltiple puede provocar una variedad de síntomas. Entre los más frecuentes se encuentran la anemia (que afecta hasta al 35% de los pacientes), el dolor óseo (que afecta hasta al 58% de los pacientes), la hipercalcemia (que se encuentra en el 13% de los pacientes al momento del diagnóstico), la disfunción renal (que afecta entre el 40% y el 19% de los pacientes al momento del diagnóstico), la fatiga, la compresión de la médula espinal, las infecciones bacterianas recurrentes y los síntomas de hiperviscosidad.

En los pacientes de edad avanzada, el mieloma múltiple puede presentar síntomas adicionales, como hemorragias. Esto se debe a que la paraproteinemia, una proteína anormal producida por las células plasmáticas en el mieloma múltiple puede interferir con la producción de fibrina, una proteína esencial para la coagulación sanguínea. Además, la osteoporosis, una enfermedad que debilita los huesos, puede dificultar la obtención de muestras de médula ósea para el diagnóstico.

Predicción de la toxicidad de quimioterapia

Escala del Cancer and Aging Research Group

Un estudio realizado con 500 adultos mayores de 65 años con tumores sólidos desarrolló la escala del Cancer and Aging Research Group (CARG) está disponible en línea en: http://www.mycarg.org/Chemo_Toxicity_Calculator. (18,19) una herramienta que demostró la toxicidad inducida por quimioterapia en adultos mayores. (17)

La escala considera variables propias del paciente (edad, sexo), del tumor y el tratamiento (tipo de cáncer, dosis de quimioterapia, número de medicamentos), además de incluir valores de laboratorio (hemoglobina, creatinina) y variables de la valoración geriátrica integral como; caídas, actividades instrumentadas, actividad social, déficit sensorial, capacidad para caminar una cuadra. (18)

La evidencia científica y las bases de datos indican que la escala CARG es superior a las herramientas comúnmente utilizadas, como la escala de Karnofsky, para predecir la toxicidad en pacientes de oncología. La escala CARG tiene una mayor capacidad para identificar a los pacientes con un riesgo muy alto de presentar toxicidad clínica significativa. (Tabla 1)

Tabla 1

Calculadora de toxicidad del Cancer and Aging Research Group (CARG)	
Características de riesgo	Puntos
Edad $\geq$ 72 años	2
Neoplasia gastrointestinal o genitourinaria	2
Dosis estándar de quimioterapia	2
Poliquimioterapia (2 o más medicamentos)	2
Hemoglobina $<$ 11 g/dl (hombre) o $<$ 10 g/dl (mujer)	3
Aclaramiento creatinina (según fórmula de Jelliffe con peso ideal) $<$ 34 ml/min	3
Audición regular o mala	2
$\geq$ 1 caída en los últimos 6 meses	3
Requiere ayuda para tomar sus medicamentos	1
Algo limitado o muy limitado para caminar una cuadra	2
Disminución de actividad social por motivos de salud	1
Categoría de riesgo de toxicidad (incidencia de toxicidad grado 3-5)	Puntos
Bajo (30%)	0 - 5
Intermedio (52%)	6 - 9
Alto (83%)	10 - 19



La efectividad del modelo se comprobó internamente mediante un proceso de validación repetido 10 veces. El modelo logró identificar a los adultos mayores con riesgo de toxicidad por quimioterapia, mientras que la medida de estado funcional comúnmente utilizada en oncología, KPS, no lo logró.

Recordando la validez de los estudios en adultos mayores; “Esta valoración exhaustiva permite hallar déficits no encontrados en una evaluación oncológica ordinaria, y puede ayudar a predecir la supervivencia global y la toxicidad por quimioterapia” (18).

El modelo de predicción asignó puntajes de riesgo a cada variable individual. El puntaje de riesgo total para cada paciente varió entre 0 (menor riesgo de toxicidad) y 19 (mayor riesgo de toxicidad). Con base en esta puntuación, la cohorte se dividió en tres grupos: riesgo bajo (0 a 5 puntos), riesgo medio (6 a 9 puntos) y riesgo alto (10 a 19 puntos).

La evaluación de los pacientes durante el ciclo de quimioterapia incluyó la identificación de eventos adversos graves. Se consideraron eventos adversos de grado 3 (que requerían hospitalización), grado 4 (que ponían en peligro la vida) y grado 5 (muerte relacionada con el tratamiento), según la definición del Instituto Nacional del Cáncer en sus Criterios de Terminología Común para Eventos Adversos, versión 3.0.15. (Anexos)

Los resultados de los estudios, que confirman el alto riesgo de toxicidad de la quimioterapia en adultos mayores, coinciden con investigaciones anteriores (15,16). Diversos factores podrían explicar este fenómeno. En primer lugar, con la edad, las reservas fisiológicas en todos los sistemas orgánicos disminuyen, lo que afecta la capacidad del cuerpo para tolerar el tratamiento. El envejecimiento se asocia con una menor reserva de médula ósea y un mayor riesgo de mielosupresión inducida por quimioterapia (13,14). Además, la función renal alterada, común en adultos mayores, puede afectar el aclaramiento de la quimioterapia (12). Por último, factores prácticos pueden influir en la adherencia a los cuidados de apoyo. Por ejemplo, los pacientes con un sistema de apoyo deficiente podrían tener menos probabilidades de buscar atención médica cuando experimentan efectos adversos.



La evaluación geriátrica puede influir significativamente en las decisiones de tratamiento para pacientes con cáncer. Un estudio demostró que esta evaluación modifica las decisiones en hasta el 50% de los casos (11). En vista de esto, la Sociedad Internacional de Oncología Geriátrica y la Red Nacional Integral del Cáncer recomiendan realizar una evaluación geriátrica de detección a todos los adultos mayores con cáncer (9,10).

La posibilidad de toxicidad grave durante la quimioterapia es un factor crucial que los oncólogos evalúan al elegir un plan de tratamiento. En pacientes mayores con cánceres avanzados, entre el 25% y el 60% reciben una reducción de la dosis planeada para su primer ciclo de quimioterapia.

La práctica habitual de reducir la dosis de quimioterapia en pacientes mayores con base en la edad cronológica y el estado funcional ECOG ha demostrado ser ineficaz para predecir el riesgo de toxicidad o la tolerabilidad del tratamiento.

La clasificación de la severidad, que consta de 5 grados:

G° 0 = ausencia de toxicidad

G° 1 = toxicidad leve

G° 2 = toxicidad moderada

G° 3 = toxicidad severa e indeseable

G° 4 = toxicidad que amenaza la vida o incapacita de forma importante

G° 5 = muerte tóxica

Tratamiento antineoplásico

El tratamiento en los pacientes ancianos con diagnóstico de neoplasia es complejo. Existen limitaciones para su inclusión en ensayos terapéuticos, especialmente la pertenencia al grupo etario y la presencia de múltiples comorbilidades. (7)

El abordaje terapéutico principal en el anciano consiste en mejorar la calidad de vida y establecer un esquema de tratamiento antineoplásico con baja toxicidad. (2)



Los cambios en la farmacodinamia se reflejan tanto en la actividad antineoplásica como en los efectos secundarios de los medicamentos citotóxicos. Se describen tres mecanismos de resistencia farmacológica: aumento en la expresión de glicoproteína-p, disminución en la apoptosis y menor angiogénesis. Algunos mecanismos causan incremento de toxicidad y disminución de la reserva de células madre (repercute en tejido hematopoyético y epitelial principalmente), disminución del catabolismo, disminución del tejido funcional (mayor susceptibilidad a falla orgánica, en particular a nivel neurológico o cardíaco). (3)

Las principales complicaciones por toxicidad celular en los ancianos son mielosupresión (disminución en las tres líneas celulares), mucositis, afección en la funcionalidad cardíaca, neuropatía periférica, afección neurológica central (delirium, disfunción cerebelosa, disminución cognitiva progresiva). (4, 5,3)

Posterior a identificar el pronóstico del paciente debe puntualizarse si el tratamiento proporcionará más beneficio que riesgo, si el paciente está en condiciones de tolerar el tratamiento y sobre todo hacer énfasis en las condiciones relacionadas con el proceso de envejecimiento (esperanza de vida, reserva funcional y apoyo social). (2, 4,6)



2. PLANTEAMIENTO DEL PROBLEMA

El cáncer en el adulto mayor cobra más importancia y seguirá a la alta debido al aumento población y a la alta esperanza de vida alcanzada. La falta de médicos formados en el área de Geriatría y la pobre formación académica en las universidades en materia de Geriatría no es suficiente para afrontar la complejidad de tratamiento para este grupo etario.

Demostrar el estado funcional con las escalas básicas no permite determinar con precisión los posibles efectos adversos de la farmacoterapia.

Se realizó una búsqueda en la consulta de hematoncológica del centro de Cancerología de Chihuahua , de los pacientes que cumplen con los criterios de ingreso, así como búsqueda en los archivos de laboratorio de los resultados de los pacientes durante su primera valoración en hematoncológica, previo a tratamiento con quimioterapia, corroborando con información posterior a recibir tratamiento en búsqueda de alteraciones y reacciones adversas a manejo, con la intención de evidenciar que el cálculo de probabilidad de quimiotoxicidad pudo evitar los efectos adversos del tratamiento farmacológico al considerar la reducción de dosis en los pacientes seleccionados.



3. JUSTIFICACIÓN

La quimioterapia diseñada para salvar vidas y combatir células cancerosas, puede ser contraproducente en ciertos individuos, llegando a intolerancia y toxicidad por la misma, siendo de mayor importancia para el paciente de mayor edad. La apariencia y la edad cronológica no son factores confiables para medir el riesgo de efectos secundarios por quimioterapia.

Es de notar que nuestra nación se encuentra en proceso de envejecimiento poblacional con un aumento exponencial de adultos mayores, gracias a las bajas tasas de mortalidad y fecundidad, esto es de interés, la prevención primaria para un envejecimiento saludable en nuestra población ha fracasado repercutiendo en un grupo etario pluripatológico con un daño acumulativo difícil de determinar y una variabilidad en farmacodinamia y farmacocinética condicionado a los procesos de envejecimiento individuales, lo cual coloca a nuestros adultos mayores en un estado vulnerable subestimado, esto agregado a un proceso neoplásico resalta más la vulnerabilidad de nuestros pacientes y la proyección a sufrir efectos secundarios o tóxicos de sus tratamientos médicos.

Aunque contamos con una valoración geriátrica integral la cual puede demostrar un estimado individual del daño acumulativo, llevarla a la práctica resulta difícil dado la falta de personal en geriatría dentro de los centros oncológicos, la sobrecarga de trabajo de los médicos especialistas en hematología y el poco tiempo del que disponen para la toma de decisiones para la determinación de manejo.

Contar con una herramienta efectiva que nos ayude a determinar el alto riesgo y la vulnerabilidad en los pacientes dependiendo de su situación funcional, comorbilidades y resultados bioquímicos, se convierte en algo indispensable en el medio médico. Dando una solución práctica que sea fácil de usar por cualquier facultativo y sea un predictor efectivo al menos para la toxicidad grave, que puede llevar a hospitalización del paciente y empeoramiento de su estado basal.



El uso de la calculadora CARG, como método de detección de los pacientes con riesgo potencial de quimiotoxicidad, disminuirá días de internamiento hospitalario, los costes de internamiento y optimización del tiempo del médico en la toma de decisiones al momento de determinar un esquema estándar o reducido en el uso de quimioterapia. Esperando la determinación y prevención hasta en el 80% de los casos de quimiotoxicidad.



4. HIPÓTESIS

El uso de la escala del Cancer and Aging Research Group (CARG), es una herramienta de detección, practica y precisa para el adulto mayor con cáncer hematológico y riesgo elevado de presentar quimiotoxicidad grado 3 o más.

5. OBJETIVOS

Objetivo general

Detectar al paciente con riesgo de quimiotoxicidad en cáncer hematológico usando la escala CARG, así como conocer el porcentaje de éxito en detección

Objetivos específicos

Determinar el porcentaje de éxito en detección de pacientes con alto riesgo de toxicidad.

Determinar grupo por sexo más propenso a sufrir quimiotoxicidad.

Determinar el tipo de toxicidad más frecuente encontrado posterior a dosis de quimioterapia.



6. MATERIAL Y MÉTODOS

6.1 Tipo de estudio:

Estudio observacional retrospectivo.

6.2 Diseño de estudio:

Analítico

6.3 Tipo de población:

Pacientes adultos mayores atendidos en el centro de Cancerología de Chihuahua los cuales cumplen con la definición de caso confirmado de cáncer hematológico

6.4 Lugar de realización:

Centro de cancerología del Estado de Chihuahua



6.5 Criterios de selección

Criterios de Inclusión:

- Pacientes mayores de 65 años.
- Diagnóstico confirmado de neoplasia hematológica.
- Primera consulta externa en oncología médica de forma ambulatoria.
- Aceptación de participar en el estudio, con consentimiento informado por escrito.
- Iniciar tratamiento oncológico activo con quimioterapia.

Criterios de No inclusión:

- Incumplimiento de los criterios de inclusión.
- Incapacidad para realizar las pruebas por comorbilidad severa.
- Pacientes que realicen tratamiento dirigido, con inmunoterapia, hormonoterapia o sintomático exclusivamente.
- Revocación del consentimiento informado



6.6 Tamaño de muestra

Se incluirá a todas las pacientes que cumplan con la definición de la población a estudiar y con los criterios de inclusión durante el período comprendido de 1 de junio del 2020 al 1 de junio del 2023.

Nivel de confianza: 95%

Se calcula un tamaño de muestra utilizando el programa EPI INFO considerando un nivel de confianza del 95% y un margen de error de un 5%. Teniendo una población de 43 pacientes los cuales cumplen con los criterios de selección mencionados previamente para un total de $N= 42$ pacientes.

6.7 Operacionalización de variables de estudio

Variable independiente

VARIABLE	DEFINICIÓN	TIPO DE VARIABLE	ESCALA DE MEDICIÓN	INDICADOR
Cáncer hematológico	Confirmación de cáncer de origen hematológico.	Cualitativo	Dicotómica	Prueba de laboratorio positiva o confirmación con biopsia.
Edad	Edad cronológica al momento del diagnóstico	Cuantitativo	Discreta	Edad mayor a 65 años
Sexo	Sexo biológico del paciente	Cualitativo	Nominal	Hombre Mujer
Puntuación de escala CARG	Realiza la estimación de riesgo en base	Cualitativa	Politémica ordenada	Riesgo bajo 0-5 puntos Riesgo intermedio 6-9 puntos



	al obtenido	puntaje		Riesgo alto 10-19 puntos
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Variable dependiente

VARIABLE	DEFINICIÓN	TIPO DE VARIABLE	ESCALA DE MEDICIÓN	INDICADOR
Toxicidad	Efectos secundarios relacionados al uso de quimioterapia.	Cualitativa	Dicotómica	Las características definidas en el anexo 3 1; G° 0 = ausencia de toxicidad G° 1 = toxicidad leve G° 2 = toxicidad moderada G° 3 = toxicidad severa e indeseable G° 4 = toxicidad que amenaza la

				vida o incapacita de forma importante G° 5 = muerte tóxica
Tratamiento con quimioterapia	El uso de fármacos para destruir las células cancerosas. Este tipo de tratamiento contra el cáncer actúa evitando que las células cancerosas crezcan, se dividan y	Cualitativo	Nominal	El paciente recibió dosis estándar de quimioterapia o dosis reducida.



	formen más células.			
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6.8 Recursos

HUMANOS:

- Autor: Dr. Eloy Garza Ramos
- Director: Dr. Yuri Guzmán Lara
- Médicos y enfermeras del Centro de Cancerología de Chihuahua

FISICOS:

- Monitor de signos vitales.
- Hojas de consentimiento informado.
- Jeringas para toma de muestra de laboratorio.
- Tubos para toma muestras de laboratorio.
- Computadora.
- Equipo para venoclisis.
- Guantes estériles de látex.
- Hojas de recolección de datos

FINANCIEROS:

RECURSO	PRECIO
Jeringa para toma de muestra	\$47.36
Equipo para venoclisis	\$70.93
Computadora	\$14,999
Tubo para toma de muestra	\$58
Guantes estériles	\$511.33
Total	\$15686.62



6.9 Consideraciones éticas

Este estudio se apegará a lo señalado por la Declaración de Helsinki, principios éticos para las investigaciones médicas en seres humanos y lo dispuesto en la Ley General de Salud en materia de investigación. Se someterá ante el Comité Local de investigación y al comité de Ética de Investigación Institucional. Se protegerá la confidencialidad de la información y se recabará consentimiento informado (ANEXO 1).

Se obtendrá consentimiento Institucional del Hospital Central del Estado de la Ciudad de Chihuahua para la realización del protocolo de investigación.

En la relación médico-paciente es importante el conocimiento del consentimiento informado, representado por el procedimiento médico formal, una exigencia ética y un derecho reconocido, cuyo objetivo es la manifestación del paciente de aceptar o no la realización de un determinado procedimiento, previo al conocimiento médico del diagnóstico, los procedimientos para el tratamiento de la enfermedad y las posibles implicaciones derivadas del manejo e incluso las consecuencias en el evento de no ser intervenido.

Se cumplirá con la Norma Oficial Mexicana NOM-004-SSA3-2012, del expediente clínico donde se recabará el documento denominado Carta de Consentimiento Informado por escrito firmados por el paciente o su representante legal o familiar más cercano en vínculo, mediante el cual se acepta un procedimiento médico o quirúrgico con fines diagnósticos, terapéuticos, rehabilitar, paliativos o de investigación una vez que se ha recibido información de los riesgos y beneficios esperados para el paciente.

El presente estudio está enfocado en el control del dolor postquirúrgico de las pacientes sometidas a cesárea, vinculado en primera instancia a brindar una mejor calidad de atención hospitalaria con un adecuado tratamiento bajo vigilancia del médico anestesiólogo y residente de la especialidad de Anestesiología durante el periodo perioperatorio, transoperatorio y postoperatorio.



El paciente fue informado de los objetivos, métodos, beneficios y posibles riesgos inherentes al estudio.

7. ANÁLISIS ESTADÍSTICO

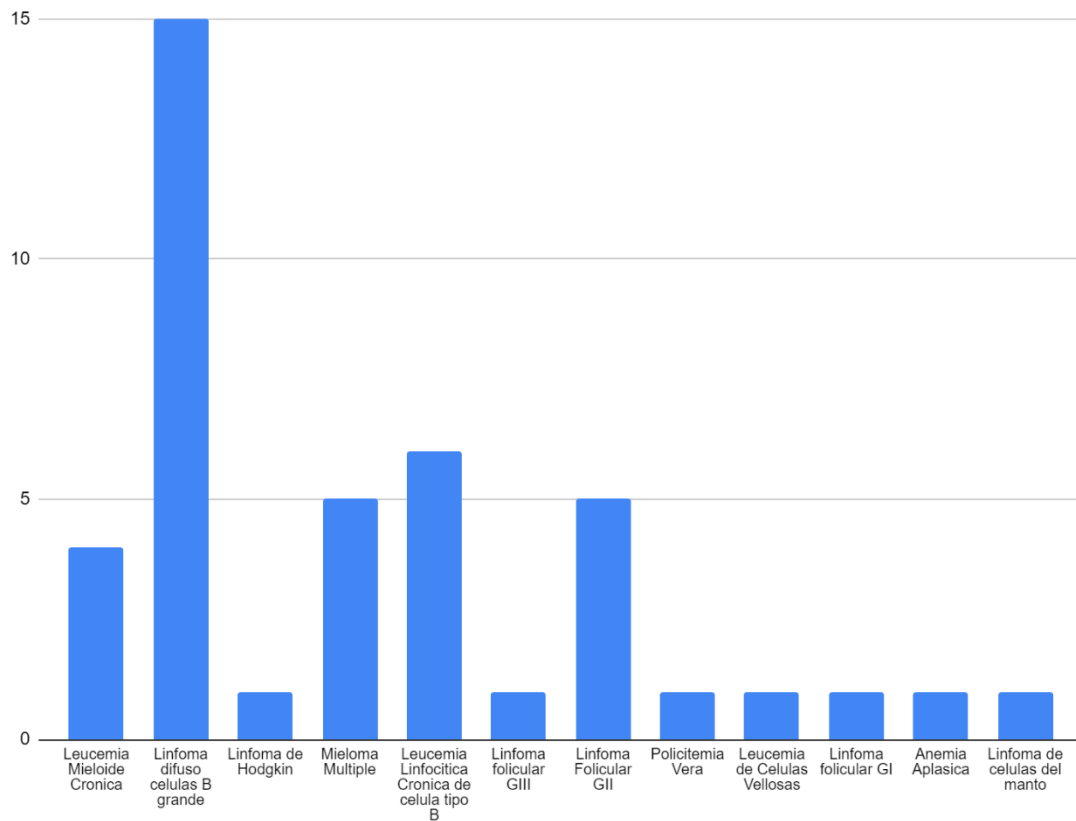
Para efectuar el análisis estadístico se empleó el programa IBM SPSS v27 (USA). Los resultados fueron colocados en tablas y gráficos. Para revisar las variables cualitativas se emplearon frecuencias y porcentajes; mientras que para variables cuantitativas se usaron medidas de tendencia central. El análisis inferencial se realizó con valor de Chi-cuadrada de Pearson; el valor significativo se consideró cuando $p \leq 0.05$.

8. RESULTADOS

Se estudió un total de 42 pacientes, los cuales cumplieron con los criterios de inclusión previamente mencionados en este documento, se les realizó laboratorios por parte del servicio de laboratorio clínico del Centro Estatal de Cancerología de Chihuahua.

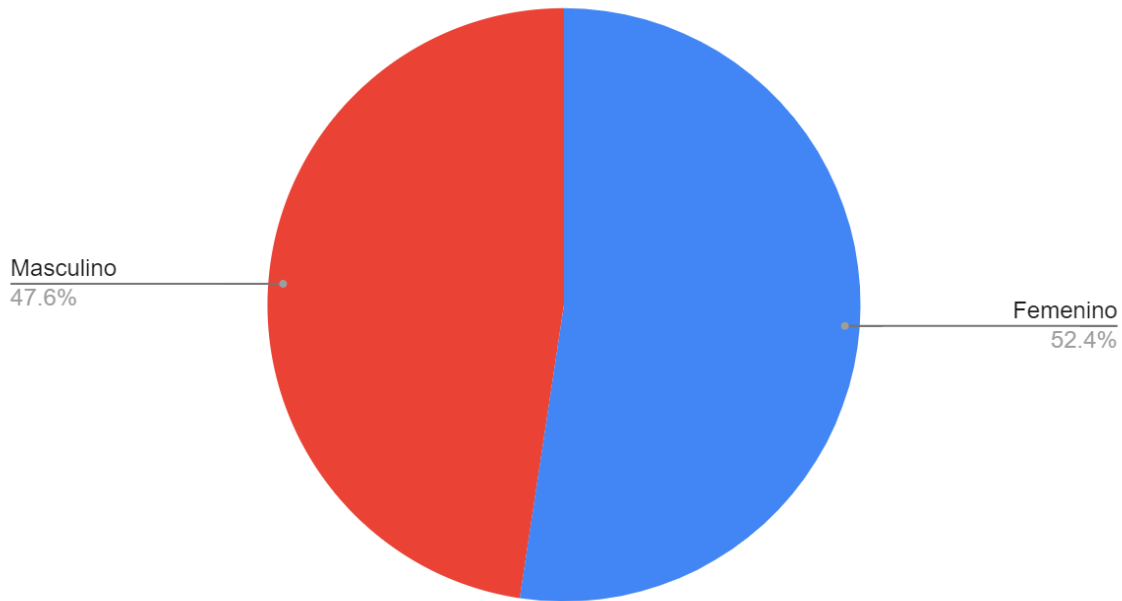
Dentro de la distribución de diagnósticos que se tomaron para este estudio se observó un mayor número de casos de Linfoma difuso de células B grande con un total de 15 pacientes, llegando a superar por más del doble al segundo diagnóstico más frecuentes en este estudio que es Leucemia linfocítica crónica. (Figura 1).

Figura 1. distribución por diagnóstico



En cuanto la distribución por sexo, los hombres representan la menor parte de la población estudiada con un total de 20 pacientes, lo que representa 47.6%, siendo los 22 pacientes restantes del sexo femenino representando el 52.4% del total (Figura 2).

Figura 2. Distribución por sexo



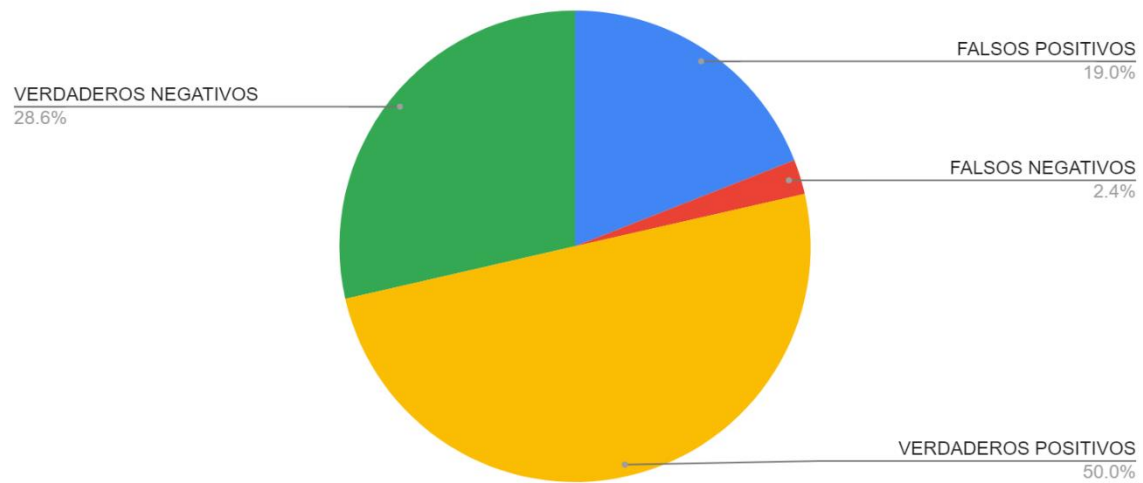
De los 42 pacientes, 13 fueron clasificados como riesgo elevado según los criterios utilizados por la calculadora de CARG, de los cuales 10 fueron verdaderamente positivos a toxicidad y contaban con la clasificación de alto riesgo.

Es de llamar la atención que 16 de los pacientes que fueron clasificados en riesgo intermedio de los cuales solo 11 presentaron toxicidad a quimioterapia reportada. Esto predispone los resultados a una correlación moderada entre donde la relación es significativa, pero no perfecta. Los pacientes clasificados en bajo riesgo fueron un total de 13, teniendo solo 1 de ellos reacción de toxicidad, estos resultados son representados en la tabla 2, tomando en cuenta que, a partir de la clasificación de riesgo intermedio y riesgo alto, se esperaba la reacción de toxicidad, los pacientes que no presentaron toxicidad en estos grupos fueron clasificados como falsos positivos (figura3). Se estima que la sensibilidad obtenida de la clasificación es de 95 %, con una especificidad de 60%, un valor predictivo positivo de 72.41 % y un valor predictivo negativo de 92.30%.

Tabla 2.

TOTAL, DE RESULTADOS	
FALSOS POSITIVOS	8
FALSOS NEGATIVOS	1
VERDADEROS POSITIVOS	21
VERDADEROS NEGATIVOS	12

Figura 3



Dentro de la estadificación de riesgo en relación con la presencia de toxicidad, se realizó la asociación de los resultados obteniendo un valor de significancia < 0.001

Tabla cruzada Toxicidad*Clasificación

			Clasificación			
			1.00	2.00	3.00	Total
Toxicidad	1.00	Recuento	11	6	3	20
		% dentro de Toxicidad	55.0%	30.0%	15.0%	100.0%
	2.00	Recuento	1	10	11	22
		% dentro de Toxicidad	4.5%	45.5%	50.0%	100.0%
Total	Recuento		12	16	14	42
	% dentro de Toxicidad		28.6%	38.1%	33.3%	100.0%

Pruebas de chi-cuadrado

	Valor	gl	Significación asintótica (bilateral)
Chi-cuadrado de Pearson	13.841 ^a	2	<.001
Razón de verosimilitud	15.527	2	<.001
Asociación lineal por lineal	12.108	1	<.001
N de casos válidos	42		

a. 0 casillas (0.0%) han esperado un recuento menor que 5. El recuento mínimo esperado es 5.71.

Medidas simétricas

		Valor	Error estándar asintótico ^a	T aproximada ^b	Significación aproximada
Intervalo por intervalo	R de Pearson	.543	.117	4.094	<.001 ^c
Ordinal por ordinal	Correlación de Spearman	.539	.120	4.051	<.001 ^c
N de casos válidos		42			

a. No se presupone la hipótesis nula.

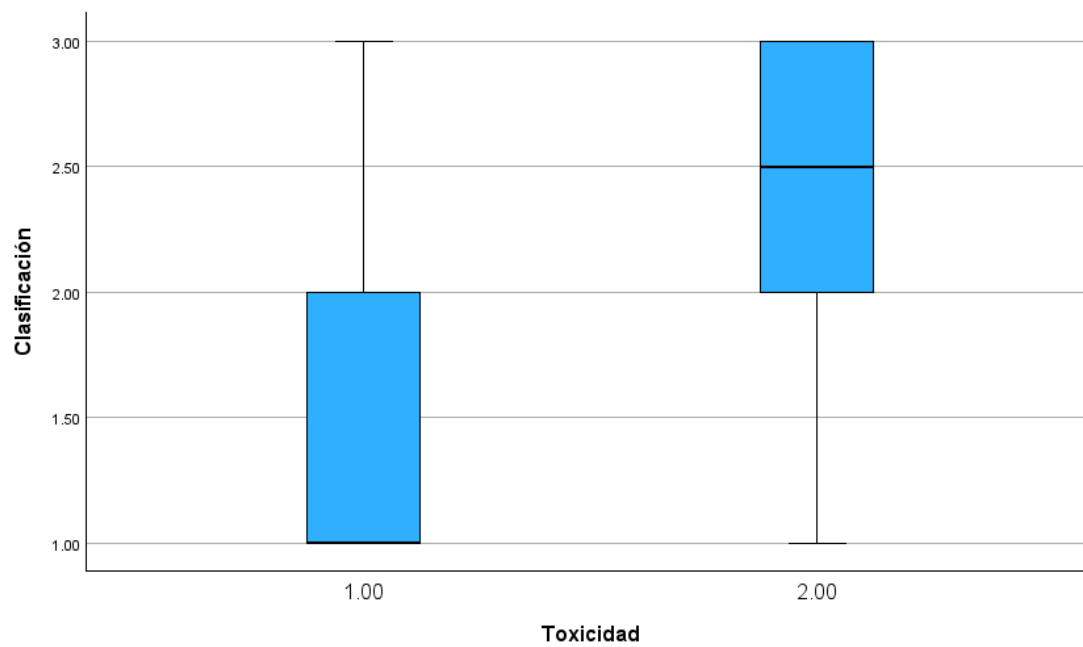
b. Utilización del error estándar asintótico que presupone la hipótesis nula.

c. Se basa en aproximación normal.

Correlaciones

			Clasificación	Toxicidad
Rho de Spearman	Clasificación	Coefficiente de correlación	1.000	.539**
		Sig. (bilateral)	.	<.001
		N	42	42
	Toxicidad	Coefficiente de correlación	.539**	1.000
		Sig. (bilateral)	<.001	.
		N	42	42

** . La correlación es significativa en el nivel 0,01 (bilateral).



Resumen de procesamiento de casos

		Recuento	Porcentaje marginal
CATEGORIA DE RIESGO	Bajo riesgo	13	31.0%
	Riesgo alto	13	31.0%
	Riesgo intermedio	16	38.1%
FALSOS POSITIVOS Y NEGATIVOS	Falso Negativo	1	2.4%
	Falso Positivo	8	19.0%
	Verdadero Negativo	12	28.6%
	Verdadero Positivo	21	50.0%
SEXO	F	22	52.4%
	M	20	47.6%
DIAGNOSTICO	Anemia Aplasica	1	2.4%
	Leucemia de Celulas Vellosas	1	2.4%
	Leucemia Linfocitica Cronica de celula tipo B	6	14.3%
	Leucemia Mieloide Cronica	4	9.5%
	Linfoma de celulas del manto	1	2.4%
	Linfoma de Hodgkin	1	2.4%
	Linfoma difuso celulas B grande	15	35.7%
	Linfoma folicular GI	1	2.4%
	Linfoma Folicular GII	5	11.9%
	Linfoma folicular GIII	1	2.4%
	Mieloma Multiple	5	11.9%
	Policitemia Vera	1	2.4%
TIPO DE TOXICIDAD	CARDIOVASCULAR	3	7.1%
	ENDOCRINOLOGICA	3	7.1%
	HEMATOLOGICA	1	2.4%
	HEPATICA	1	2.4%
	MUCOSAS	1	2.4%
	NEUROLOGICA	7	16.7%
	NINGUNA	20	47.6%
	OSEA	2	4.8%
	OSEA Y NEUROLOGICA	3	7.1%
	RENAL	1	2.4%
Válido		42	100.0%
Excluido		23	
Total		65	

CATEGORIA DE RIESGO

	Frecuencia	Porcentaje	Porcentaje válido	Porcentaje acumulado
Válido	23	35.4	35.4	35.4
Bajo riesgo	13	20.0	20.0	55.4
Riesgo alto	13	20.0	20.0	75.4
Riesgo intermedio	16	24.6	24.6	100.0
Total	65	100.0	100.0	

Los valores bioquímicos observados en las pacientes se muestran en las siguientes tablas.

Estadísticos descriptivos

	N	Mínimo	Máximo	Media	Desv. estándar
HEMOGLOBINA	42	4.2	18.1	12.081	2.8143
ACLARAMIENTO DE CREATININA	42	34,764719930	109,79571290	79,912143994	15,318647843
N válido (por lista)	42				

Estadísticos

	HEMOGLOBINA	ACLARAMIENTO DE CREATININA
N	Válido 42	42
	Perdidos 23	23
Media	12.081	79,912143994
Error estándar de la media	.4343	2,3637186790
Mediana	11.950	82,964318880
Desv. estándar	2.8143	15,318647843
Varianza	7.920	234.661
Rango	13.9	75,030992970
Mínimo	4.2	34,764719930
Máximo	18.1	109,79571290

En cuanto a la asociación de los valores bioquímicos con el reporte de toxicidad se realizó una prueba de Chi-cuadrada de Pearson, los valores de p para los resultados de hemoglobina. Se tomaron como valor de corte los establecidos por la calculadora de CARG, se clasificaron los resultados como normales o bajos, no se siguieron asociaciones estadísticamente significativas, el valor de chi cuadrado es

bajo y la significancia es alta, lo que sugiere que cualquier asociación observada entre la hemoglobina y la toxicidad es probablemente el resultado del azar y no indica una relación real entre las dos variables.

Pruebas de chi-cuadrado

	Valor	gl	Significación asintótica (bilateral)	Significación exacta (bilateral)	Significación exacta (unilateral)
Chi-cuadrado de Pearson	.016 ^a	1	.900		
Corrección de continuidad ^b	.000	1	1.000		
Razón de verosimilitud	.016	1	.900		
Prueba exacta de Fisher				1.000	.620
Asociación lineal por lineal	.016	1	.901		
N de casos válidos	42				

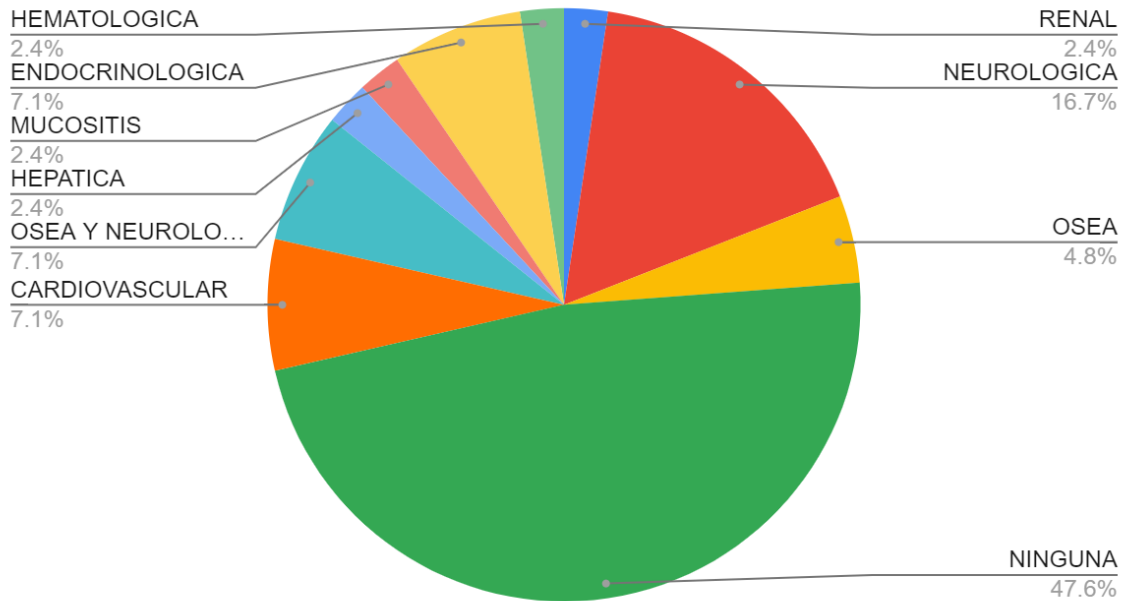
a. 2 casillas (50.0%) han esperado un recuento menor que 5. El recuento mínimo esperado es 2.86.

b. Sólo se ha calculado para una tabla 2x2

Los resultados de depuración de creatinina. Se tomaron como valor de corte los establecidos por la calculadora de CARG, dado que todos los pacientes durante el estudio superaron el corte de depuración (34 ml/min), no se puede establecer una asociación para realizar pruebas de chi cuadrado.

Dentro de los tipos de toxicidad reportados observamos como principal reporte neurotoxicidad asociada a quimioterapia, la presenta una incidencia el doble al resto de los tipos de toxicidad, podemos observar un grupo especial donde se reportó la combinación de toxicidad ósea y neurológica simultáneamente.

Reporte de toxicidad



9. DISCUSIÓN

Aunque tenemos la limitante de pocos estudios concluyentes de predictores de toxicidad en el adulto mayor y el número reducido de personal en el área de oncogeriatría, diversos métodos de la valoración general y auto reporte de los pacientes en sus actividades durante la entrevista médica pueden ayudar a dar una estimación en la clasificación de riesgo.

Observamos en los resultados que existe muy poca diferencia en la cantidad de pacientes con respecto al sexo existe una mayor distribución en los pacientes con Linfoma difuso de célula B grande, lo interesante del estudio es que los pacientes que por medio de la calculadora fueron estadificados en riesgo intermedio, fueron los presentaron una asociación moderada positiva al desarrollo de toxicidad. Aunque de manera general existe relación significativa entre la estadificación y el desarrollo de toxicidad, la zona gris (riesgo intermedio) presento una tendencia modesta.



Con respecto a la estadificación de riesgo y la toxicidad, basado en la muestra de datos utilizada en el análisis, se estima que el error estándar del estadístico calculado es aproximadamente 0.117 unidades. Esto indica la dispersión esperada en las estimaciones, si se tomaran múltiples muestras de tamaño similar de la población.

De manera global encontramos una correlación moderada entre las variables, pero no extremadamente fuerte. Con un valor positivo de Spearman lo que significa que a medida que aumenta la estadificación de riesgo aumenta la incidencia de toxicidad, lo cual lo podemos observar en nuestra grafica de cajas, sin implicar casualidad.

Sí valoramos los datos obtenidos nos damos cuenta de que se logró identificar correctamente el 95% de los casos positivos (sensibilidad), sin embargo, obtuvimos una identificación modesta de los casos negativos (especificidad de 60%), entre todos los casos que clasificamos como positivos, 72% fueron realmente positivos a toxicidad y de los que estadificamos como negativos, 92% fueron realmente negativos.

En los parámetros de laboratorio utilizados en la calculadora de estadificación, los niveles de hemoglobina son en los que se observó menor dispersión, con mejor correlación que con el aclaramiento de creatinina, a pesar de ello el parámetro bioquímico de hemoglobina tiene una correlación baja. El aclaramiento de creatinina, tomando en cuenta el corte de la calculadora ningún paciente de los estudiados obtuvo puntos en dicho rubro y en los que los datos sugieren que debido al rango que obtuvimos y la gran dispersión de datos en el aclaramiento de creatinina, observamos un umbral de corte en la calculadora de estadificación muy bajo para el aclaramiento de creatinina.



10. CONCLUSIÓN

En los últimos años existe la tendencia a un incremento en el cáncer del adulto mayor, el cáncer hematológico entre ellos. A pesar de la elevada morbilidad de este grupo de edad, como la población estudiada en esta investigación, el utilizar dosis estándar de quimioterapia en todos los pacientes, predispone al aumento de morbilidad, lo cual nos aleja del objetivo inicial por el cual inicio tratamiento quimioterapéutico. La falta de personal médico especializado en los centros especializados en la atención de cáncer complica más la situación y toma de decisiones.

Debido a que no existe una manera universal y directa de poder estadificar a los pacientes podemos utilizar diferentes métodos, utilizar el método más fácil, simple y reproducible por los todos los médicos es el ideal.

En esta investigación comprobamos que, aunque tenemos una zona gris (riesgo intermedio) en la estadificación, podemos tomar en cuenta la calculadora CARG para la toma de decisiones rápidas y reproducibles sobre todo con los resultados de correlación fuerte como lo son riesgo bajo y riesgo alto.

Durante la investigación, se evidencio que el umbral bajo que se toma en cuenta para asignar puntos en el aclaramiento de creatinina (34 ml/min) resulto poco útil y pobremente relacionado, la hemoglobina la cual figuraba como un parámetro bioquímico de mayor confianza presento una correlación baja la cual de la misma manera solamente se estadifica en un punto de corte el cual es 10 g/dl, se deben continuar realizado más estudios para determinar agregar nuevos puntos de corte en ambos parámetros en busca de mejorar la relación positiva.

La investigación puede concluir que, el uso del cálculo de estadificación con parámetros simples y reproducibles, a fin de que sea más fácil para el facultativo, puede ser tomado en cuenta sobre todo al momento de tener resultados como bajo riesgo o riesgo alto, con ellos determinar la dosis estándar o dosis reducida de quimioterapia, esto con la final de disminuir efectos adversos y complicaciones posteriores de los pacientes.



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12.ANEXOS

Anexo 12.1. Hoja de recolección

Datos generales;

Nombre: _____

Edad: _____ escolaridad: _____ ocupación: _____

Sexo: _____

Dirección: _____

Teléfono: _____

Última hospitalización: _____

Enfermedad hematológica diagnosticada: _____

Fecha de diagnóstico; _____

Dosis de primera quimioterapia:

Tasa de filtrado glomerular:

Numero de caídas en los últimos 6 meses;

Uso de auxiliar auditivo:

Ayuda para administra medicación en casa;

Afección en sus actividades sociales;

Nivel de Hemoglobina al momento del diagnóstico:

Uso de accesorios para la marcha;

Dependencia de terceros para la marcha;

Dependencia total para realización de actividades diarias:

Discapacidad física;

Puntaje de Lawton Brody;

Grado de Katz;



Enfermedades crónicas que padece;

Enfermedad crónica	Si	No
Osteoartritis		
Artritis reumatoide		
Diabetes mellitus		
Hipertensión arterial sistémica		
Otros:		



12.2 Consentimiento informado

HOSPITAL CENTRAL DEL ESTADO. SERVICIO DE GERIATRIA

Declaración de consentimiento informado

Nombre: _____ Fecha: _____

Hago constar que se me informó que se hará uso de mi información o de mi familiar (en caso de fallecimiento) en base al padecimiento, manejo y evolución, así como a los laboratorios que se realizaron durante la estancia hospitalaria, con la finalidad de realizar una investigación y mejorar el diagnóstico, así como el pronóstico de futuros pacientes.

Manifiesto que he leído y entendido la hoja de información que se me ha entregado, que he hecho las preguntas que me surgieron sobre el estudio y que he recibido información suficiente sobre el mismo. Se me ha explicado de manera clara y concisa acerca de los beneficios e inconvenientes del uso de información personal.

Comprendo que mi participación es totalmente voluntaria, que puedo revocar el consentimiento cuando quiera sin tener que explicar el motivo y sin que esto repercuta en mi atención médica actual o próxima.

Acepto ser incluida en el estudio titulado “USO DE ESCALA CARG EN PREDICCIÓN DE QUIMIOTOXICIDAD EN ADULTO MAYOR CON CÁNCER HEMATOLÓGICO ATENDIDOS EN EL CENTRO DE CANCEROLOGÍA DE CHIHUAHUA EN EL PERIODO DE 2020 A 2023.”, el cual se está realizando con el objetivo de mejorar la atención médica a los futuros pacientes con mi enfermedad o la enfermedad de mi familiar.

Nombre y Firma (Paciente o familiar)

Nombre y firma de Testigo

Nombre y Firma de Testigo

12.3 Terminología común

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: December 12, 2003

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms,

or diagnosis. A supra-ordinate term is followed by the word 'Select' and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening or disabling AE
- Grade 5 Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term — Select' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.

Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
 1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
 2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

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Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS
March 31, 2003 (<http://ctep.cancer.gov>). Publish Date: December 12, 2003

ALLERGY/IMMUNOLOGY							Page 1 of 1
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Allergic reaction/ hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing, urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death	
REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever). ALSO CONSIDER: Cytokine release syndrome/acute infusion reaction.							
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Rhinitis	Mild, intervention not indicated	Moderate, intervention indicated	—	—	—	
REMARK: Rhinitis associated with obstruction or stenosis is graded as Obstruction/stenosis of airway – Select in the PULMONARY/UPPER RESPIRATORY CATEGORY.							
Autoimmune reaction	Autoimmune reaction	Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated	Evidence of autoimmune reaction involving a non- essential organ or function (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia)	Autoimmune reaction with life-threatening consequences	Death	
ALSO CONSIDER: Colitis; Hemoglobin; Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis); Thyroid function, low (hypothyroidism).							
Serum sickness	Serum sickness	—	—	Present	—	Death	
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.							
NAVIGATION NOTE: Urticaria as an isolated symptom is graded as Urticaria (hives, welts, wheals) in the DERMATOLOGY/SKIN CATEGORY.							
Vasculitis	Vasculitis	Mild, intervention not indicated	Symptomatic, non- steroidal medical intervention indicated	Steroids indicated	Ischemic changes; amputation indicated	Death	
Allergy/Immunology – Other (Specify, __)	Allergy – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death	

AUDITORY/EAR						Page 1 of 2
		Grade				
Adverse Event	Short Name	1	2	3	4	5
NAVIGATION NOTE: Earache (otalgia) is graded as Pain – Select in the PAIN CATEGORY.						
Hearing: patients with/without baseline audiogram and enrolled in a monitoring program ¹	Hearing (monitoring program)	Threshold shift or loss of 15 – 25 dB relative to baseline, averaged at 2 or more contiguous test frequencies in at least one ear; or subjective change in the absence of a Grade 1 threshold shift	Threshold shift or loss of >25 – 90 dB, averaged at 2 contiguous test frequencies in at least one ear	Adult only: Threshold shift of >25 – 90 dB, averaged at 3 contiguous test frequencies in at least one ear Pediatric: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., ≥20 dB bilateral HL in the speech frequencies; ≥30 dB unilateral HL, and requiring additional speech-language related services)	Adult only: Profound bilateral hearing loss (>90 dB) Pediatric: Audiologic indication for cochlear implant and requiring additional speech-language related services	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Hearing: patients without baseline audiogram and not enrolled in a monitoring program ¹	Hearing (without monitoring program)	—	Hearing loss not requiring hearing aid or intervention (i.e., not interfering with ADL)	Hearing loss requiring hearing aid or intervention (i.e., interfering with ADL)	Profound bilateral hearing loss (>90 dB)	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Otitis, external ear (non-infectious)	Otitis, external	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program ¹ ; Hearing: patients without baseline audiogram and not enrolled in a monitoring program ¹ .						
Otitis, middle ear (non-infectious)	Otitis, middle	Serous otitis	Serous otitis, medical intervention indicated	Otitis with discharge; mastoiditis	Necrosis of the canal soft tissue or bone	Death

AUDITORY/EAR						
Page 2 of 2						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Tinnitus	Tinnitus	—	Tinnitus not interfering with ADL	Tinnitus interfering with ADL	Disabling	—
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program ¹ ; Hearing: patients without baseline audiogram and not enrolled in a monitoring program ¹ .						
Auditory/Ear – Other (Specify, ___)	Auditory/Ear – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

¹ Drug-induced ototoxicity should be distinguished from age-related threshold decrements or unrelated cochlear insult. When considering whether an adverse event has occurred, it is first necessary to classify the patient into one of two groups. (1) The patient is under standard treatment/enrolled in a clinical trial <2.5 years, and has a 15 dB or greater threshold shift averaged across two contiguous frequencies; or (2) The patient is under standard treatment/enrolled in a clinical trial >2.5 years, and the difference between the expected age-related and the observed threshold shifts is 15 dB or greater averaged across two contiguous frequencies. Consult standard references for appropriate age- and gender-specific hearing norms. e.g., Morrell, et al. Age- and gender-specific reference ranges for hearing level and longitudinal changes in hearing level. Journal of the Acoustical Society of America 100:1949-1967, 1996; or Shottland, et al. Recommendations for cancer prevention trials using potentially ototoxic test agents. Journal of Clinical Oncology 19:1658-1663, 2001.

In the absence of a baseline prior to initial treatment, subsequent audiograms should be referenced to an appropriate database of normals. ANSI. (1996)

American National Standard: Determination of occupational noise exposure and estimation of noise-induced hearing impairment, ANSI S 3.44-1996. (Standard S 3.44). New York: American National Standards Institute. The recommended ANSI S3.44 database is Annex B.

BLOOD/BONE MARROW						
Page 1 of 1						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Bone marrow cellularity	Bone marrow cellularity	Mildly hypocellular or $\leq 25\%$ reduction from normal cellularity for age	Moderately hypocellular or $>25 - \leq 50\%$ reduction from normal cellularity for age	Severely hypocellular or $>50 - \leq 75\%$ reduction from normal cellularity for age	—	Death
CD4 count	CD4 count	$<LLN - 500/mm^3$ $<LLN - 0.5 \times 10^9/L$	$<500 - 200/mm^3$ $<0.5 - 0.2 \times 10^9/L$	$<200 - 50/mm^3$ $<0.2 \times 0.05 - 10^9/L$	$<50/mm^3$ $<0.05 \times 10^9/L$	Death
Haptoglobin	Haptoglobin	$<LLN$	—	Absent	—	Death
Hemoglobin	Hemoglobin	$<LLN - 10.0 g/dL$ $<LLN - 6.2 mmol/L$ $<LLN - 100 g/L$	$<10.0 - 8.0 g/dL$ $<6.2 - 4.9 mmol/L$ $<100 - 80g/L$	$<8.0 - 6.5 g/dL$ $<4.9 - 4.0 mmol/L$ $<80 - 65 g/L$	$<6.5 g/dL$ $<4.0 mmol/L$ $<65 g/L$	Death
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'] schistocytes)	Evidence of red cell destruction and ≥ 2 gm decrease in hemoglobin, no transfusion	Transfusion or medical intervention (e.g., steroids) indicated	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)	Death
ALSO CONSIDER: Haptoglobin; Hemoglobin.						
Iron overload	Iron overload	—	Asymptomatic iron overload, intervention not indicated	Iron overload, intervention indicated	Organ impairment (e.g., endocrinopathy, cardiopathy)	Death
Leukocytes (total WBC)	Leukocytes	$<LLN - 3000/mm^3$ $<LLN - 3.0 \times 10^9/L$	$<3000 - 2000/mm^3$ $<3.0 - 2.0 \times 10^9/L$	$<2000 - 1000/mm^3$ $<2.0 - 1.0 \times 10^9/L$	$<1000/mm^3$ $<1.0 \times 10^9/L$	Death
Lymphopenia	Lymphopenia	$<LLN - 800/mm^3$ $<LLN \times 0.8 - 10^9/L$	$<800 - 500/mm^3$ $<0.8 - 0.5 \times 10^9/L$	$<500 - 200/mm^3$ $<0.5 - 0.2 \times 10^9/L$	$<200/mm^3$ $<0.2 \times 10^9/L$	Death
Myelodysplasia	Myelodysplasia	—	—	Abnormal marrow cytogenetics (marrow blasts $\leq 5\%$)	RAEB or RAEB-T (marrow blasts $>5\%$)	Death
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	$<LLN - 1500/mm^3$ $<LLN - 1.5 \times 10^9/L$	$<1500 - 1000/mm^3$ $<1.5 - 1.0 \times 10^9/L$	$<1000 - 500/mm^3$ $<1.0 - 0.5 \times 10^9/L$	$<500/mm^3$ $<0.5 \times 10^9/L$	Death
Platelets	Platelets	$<LLN - 75,000/mm^3$ $<LLN - 75.0 \times 10^9/L$	$<75,000 - 50,000/mm^3$ $<75.0 - 50.0 \times 10^9/L$	$<50,000 - 25,000/mm^3$ $<50.0 - 25.0 \times 10^9/L$	$<25,000/mm^3$ $<25.0 \times 10^9/L$	Death
Splenic function	Splenic function	Incidental findings (e.g., Howell-Jolly bodies)	Prophylactic antibiotics indicated	—	Life-threatening consequences	Death
Blood/Bone Marrow – Other (Specify, ___)	Blood – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC ARRHYTHMIA							Page 1 of 2
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Conduction abnormality/atrioventricular heart block – Select: – Asystole – AV Block-First degree – AV Block-Second degree Mobitz Type I (Wenckebach) – AV Block-Second degree Mobitz Type II – AV Block-Third degree (Complete AV block) – Conduction abnormality NOS – Sick Sinus Syndrome – Stokes-Adams Syndrome – Wolff-Parkinson-White Syndrome	Conduction abnormality – Select	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death	
Palpitations	Palpitations	Present	Present with associated symptoms (e.g., lightheadedness, shortness of breath)	—	—	—	
REMARK: Grade palpitations only in the absence of a documented arrhythmia.							
Prolonged QTc interval	Prolonged QTc	QTc >0.45 – 0.47 second	QTc >0.47 – 0.50 second; ≥0.06 second above baseline	QTc >0.50 second	QTc >0.50 second; life-threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	Death	
Supraventricular and nodal arrhythmia – Select: – Atrial fibrillation – Atrial flutter – Atrial tachycardia/Paroxysmal Atrial Tachycardia – Nodal/Junctional – Sinus arrhythmia – Sinus bradycardia – Sinus tachycardia – Supraventricular arrhythmia NOS – Supraventricular extrasystoles (Premature Atrial Contractions; Premature Nodal/Junctional Contractions) – Supraventricular tachycardia	Supraventricular arrhythmia – Select	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death	
NAVIGATION NOTE: Syncope is graded as Syncope (fainting) in the NEUROLOGY CATEGORY.							

CARDIAC ARRHYTHMIA							Page 2 of 2
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Vasovagal episode	Vasovagal episode	—	Present without loss of consciousness	Present with loss of consciousness	Life-threatening consequences	Death	
Ventricular arrhythmia – Select: – Bigeminy – Idioventricular rhythm – PVCs – Torsade de pointes – Trigeminy – Ventricular arrhythmia NOS – Ventricular fibrillation – Ventricular flutter – Ventricular tachycardia	Ventricular arrhythmia – Select	Asymptomatic, no intervention indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death	
Cardiac Arrhythmia – Other (Specify, ___)	Cardiac Arrhythmia – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death	

CARDIAC GENERAL							Page 1 of 3
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
NAVIGATION NOTE: Angina is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.							
Cardiac ischemia/infarction	Cardiac ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	Death	
Cardiac troponin I (cTnI)	cTnI	—	—	Levels consistent with unstable angina as defined by the manufacturer	Levels consistent with myocardial infarction as defined by the manufacturer	Death	
Cardiac troponin T (cTnT)	cTnT	0.03 – <0.05 ng/mL	0.05 – <0.1 ng/mL	0.1 – <0.2 ng/mL	0.2 ng/mL	Death	
Cardiopulmonary arrest, cause unknown (non-fatal)	Cardiopulmonary arrest	—	—	—	Life-threatening	—	
REMARK: Grade 4 (non-fatal) is the only appropriate grade. CTCAE provides three alternatives for reporting Death: 1. A CTCAE term associated with Grade 5. 2. A CTCAE 'Other (Specify, ___)' within any CATEGORY. 3. Death not associated with CTCAE term – Select in the DEATH CATEGORY.							
NAVIGATION NOTE: Chest pain (non-cardiac and non-pleuritic) is graded as Pain – Select in the PAIN CATEGORY.							
NAVIGATION NOTE: CNS ischemia is graded as CNS cerebrovascular ischemia in the NEUROLOGY CATEGORY.							
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (≥24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously Pediatric: Same as adult	Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult	Death	
REMARK: Use age and gender-appropriate normal values >95 th percentile ULN for pediatric patients.							

CARDIAC GENERAL							Page 2 of 3
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)	Death	
ALSO CONSIDER: Syncope (fainting).							
Left ventricular diastolic dysfunction	Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device or heart transplant indicated	Death	
Left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40%; SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death	
NAVIGATION NOTE: Myocardial infarction is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.							
Myocarditis	Myocarditis	—	—	CHF responsive to intervention	Severe or refractory CHF	Death	
Pericardial effusion (non-malignant)	Pericardial effusion	Asymptomatic effusion	—	Effusion with physiologic consequences	Life-threatening consequences (e.g., tamponade); emergency intervention indicated	Death	
Pericarditis	Pericarditis	Asymptomatic, ECG or physical exam (rub) changes consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; emergency intervention indicated	Death	
NAVIGATION NOTE: Pleuritic pain is graded as Pain – Select in the PAIN CATEGORY.							
Pulmonary hypertension	Pulmonary hypertension	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic hypertension, responsive to therapy	Symptomatic hypertension, poorly controlled	Death	
Restrictive cardiomyopathy	Restrictive cardiomyopathy	Asymptomatic, therapy not indicated	Asymptomatic, therapy indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death	

CARDIAC GENERAL							Page 3 of 3
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Right ventricular dysfunction (cor pulmonale)	Right ventricular dysfunction	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic cor pulmonale, responsive to intervention	Symptomatic cor pulmonale poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death	
Valvular heart disease	Valvular heart disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis; treatment other than endocarditis prophylaxis not indicated	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical therapy	Life-threatening; disabling; intervention (e.g., valve replacement, valvuloplasty) indicated	Death	
Cardiac General – Other (Specify, ___)	Cardiac General – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death	

COAGULATION							Page 1 of 1
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
DIC (disseminated intravascular coagulation)	DIC	—	Laboratory findings with <u>no</u> bleeding	Laboratory findings <u>and</u> bleeding	Laboratory findings, life-threatening or disabling consequences (e.g., CNS hemorrhage, organ damage, or hemodynamically significant blood loss)	Death	
REMARK: DIC (disseminated intravascular coagulation) must have increased fibrin split products or D-dimer. ALSO CONSIDER: Platelets.							
Fibrinogen	Fibrinogen	<1.0 – 0.75 x LLN or <25% decrease from baseline	<0.75 – 0.5 x LLN or 25 – <50% decrease from baseline	<0.5 – 0.25 x LLN or 50 – <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	Death	
REMARK: Use % decrease only when baseline is <LLN (local laboratory value).							
INR (International Normalized Ratio of prothrombin time)	INR	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—	
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – <i>Select</i> ; Hemorrhage, GU – <i>Select</i> ; Hemorrhage, pulmonary/upper respiratory – <i>Select</i> .							
PTT (Partial Thromboplastin Time)	PTT	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—	
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – <i>Select</i> ; Hemorrhage, GU – <i>Select</i> ; Hemorrhage, pulmonary/upper respiratory – <i>Select</i> .							
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])	Thrombotic microangiopathy	Evidence of RBC destruction (schistocytosis) without clinical consequences	—	Laboratory findings present with clinical consequences (e.g., renal insufficiency, petechiae)	Laboratory findings and life-threatening or disabling consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure)	Death	
REMARK: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments). ALSO CONSIDER: Creatinine; Hemoglobin; Platelets.							
Coagulation – Other (Specify, ___)	Coagulation – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death	

CONSTITUTIONAL SYMPTOMS							Page 1 of 2
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Fatigue (asthenia, lethargy, malaise)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—	
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10 ⁹ /L)	Fever	38.0 – 39.0°C (100.4 – 102.2°F)	>39.0 – 40.0°C (102.3 – 104.0°F)	>40.0°C (>104.0°F) for ≤24 hrs	>40.0°C (>104.0°F) for >24 hrs	Death	
REMARK: The temperature measurements listed are oral or tympanic. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).							
NAVIGATION NOTE: Hot flashes are graded as Hot flashes/flushes in the ENDOCRINE CATEGORY.							
Hypothermia	Hypothermia	—	35 – >32°C 95 – >89.6°F	32 – >28°C 89.6 – >82.4° F	≤28 °C 82.4°F or life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death	
Insomnia	Insomnia	Occasional difficulty sleeping, not interfering with function	Difficulty sleeping, interfering with function but not interfering with ADL	Frequent difficulty sleeping, interfering with ADL	Disabling	—	
REMARK: If pain or other symptoms interfere with sleep, do NOT grade as insomnia. Grade primary event(s) causing insomnia.							
Obesity ²	Obesity	—	BMI 25 – 29.9 kg/m ²	BMI 30 – 39.99 kg/m ²	BMI ≥40 kg/m ²	—	
REMARK: BMI = (weight [kg]) / (height [m]) ²							
Odor (patient odor)	Patient odor	Mild odor	Pronounced odor	—	—	—	
Rigors/chills	Rigors/chills	Mild	Moderate, narcotics indicated	Severe or prolonged, not responsive to narcotics	—	—	

CONSTITUTIONAL SYMPTOMS							Page 2 of 2
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Sweating (diaphoresis)	Sweating	Mild and occasional	Frequent or drenching	—	—	—	
ALSO CONSIDER: Hot flashes/flushes.							
Weight gain	Weight gain	5 – <10% of baseline	10 – <20% of baseline	≥20% of baseline	—	—	
REMARK: Edema, depending on etiology, is graded in the CARDIAC GENERAL or LYMPHATICS CATEGORIES. ALSO CONSIDER: Ascites (non-malignant); Pleural effusion (non-malignant).							
Weight loss	Weight loss	5 to <10% from baseline; intervention not indicated	10 – <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	—	—	
Constitutional Symptoms – Other (Specify, __)	Constitutional Symptoms – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death	

DEATH							Page 1 of 1
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Death not associated with CTCAE term – Select: – Death NOS – Disease progression NOS – Multi-organ failure – Sudden death	Death not associated with CTCAE term – Select	—	—	—	—	Death	
REMARK: Grade 5 is the only appropriate grade. 'Death not associated with CTCAE term – Select' is to be used where a death: 1. Cannot be attributed to a CTCAE term associated with Grade 5. 2. Cannot be reported within any CATEGORY using a CTCAE 'Other (Specify, __)'.							

DERMATOLOGY/SKIN							Page 1 of 3
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Atrophy, skin	Atrophy, skin	Detectable	Marked	—	—	—	
Atrophy, subcutaneous fat	Atrophy, subcutaneous fat	Detectable	Marked	—	—	—	
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue).							
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	Bruising	Localized or in a dependent area	Generalized	—	—	—	
Burn	Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death	
REMARK: Burn refers to all burns including radiation, chemical, etc.							
Cheilitis	Cheilitis	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	—	—	
Dry skin	Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—	
Flushing	Flushing	Asymptomatic	Symptomatic	—	—	—	
Hair loss/alopecia (scalp or body)	Alopecia	Thinning or patchy	Complete	—	—	—	
Hyperpigmentation	Hyperpigmentation	Slight or localized	Marked or generalized	—	—	—	
Hypopigmentation	Hypopigmentation	Slight or localized	Marked or generalized	—	—	—	
Induration/fibrosis (skin and subcutaneous tissue)	Induration	Increased density on palpation	Moderate impairment of function not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; very marked density, retraction or fixation	—	—	
ALSO CONSIDER: Fibrosis-cosmesis; Fibrosis-deep connective tissue.							
Injection site reaction/extravasation changes	Injection site reaction	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	—	—	
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Ulceration.							

DERMATOLOGY/SKIN							Page 2 of 3
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Nail changes	Nail changes	Discoloration; ridging (kollonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	—	—	
NAVIGATION NOTE: Petechiae is graded as Petechiae/purpura (hemorrhage/bleeding into skin or mucosa) in the HEMORRHAGE/BLEEDING CATEGORY.							
Photosensitivity	Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death	
Pruritus/itching	Pruritus	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—	
ALSO CONSIDER: Rash/desquamation.							
Rash/desquamation	Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death	
REMARK: Rash/desquamation may be used for GVHD.							
Rash: acne/acneiform	Acne	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death	
Rash: dermatitis associated with radiation – Select: – Chemoradiation – Radiation	Dermatitis – Select	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death	
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Erythema multiforme	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated	Life-threatening; disabling	Death	
Rash: hand-foot skin reaction	Hand-foot	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	—	—	

DERMATOLOGY/SKIN							Page 3 of 3
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Skin breakdown/ decubitus ulcer	Decubitus	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death	
REMARK: Skin breakdown/decubitus ulcer is to be used for loss of skin integrity or decubitus ulcer from pressure or as the result of operative or medical intervention.							
Striae	Striae	Mild	Cosmetically significant	—	—	—	
Telangiectasia	Telangiectasia	Few	Moderate number	Many and confluent	—	—	
Ulceration	Ulceration	—	Superficial ulceration <2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting)	Death	
Urticaria (hives, welts, wheals)	Urticaria	Intervention not indicated	Intervention indicated for <24 hrs	Intervention indicated for ≥24 hrs	—	—	
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).							
Wound complication, non-infectious	Wound complication, non-infectious	Incisional separation of ≤25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia	Symptomatic hernia without evidence of strangulation; fascial disruption/dehiscence without evisceration; primary wound closure or revision by operative intervention indicated; hospitalization or hyperbaric oxygen indicated	Symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death	
REMARK: Wound complication, non-infectious is to be used for separation of incision, hernia, dehiscence, evisceration, or second surgery for wound revision.							
Dermatology/Skin – Other (Specify, __)	Dermatology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death	

ENDOCRINE							Page 2 of 2
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Pancreatic endocrine: glucose intolerance	Diabetes	Asymptomatic, intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Symptoms interfering with ADL; insulin indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)	Death	
Parathyroid function, low (hypoparathyroidism)	Hypoparathyroidism	Asymptomatic, intervention not indicated	Symptomatic; intervention indicated	—	—	—	
Thyroid function, high (hyperthyroidism, thyrotoxicosis)	Hyperthyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid suppression therapy indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., thyroid storm)	Death	
Thyroid function, low (hypothyroidism)	Hypothyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma	Death	
Endocrine – Other (Specify, __)	Endocrine – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death	

GASTROINTESTINAL						
Page 1 of 10						
Adverse Event	Short Name	Grade				
		1	2	3	4	5
NAVIGATION NOTE: Abdominal pain or cramping is graded as Pain – <i>Select</i> in the PAIN CATEGORY.						
Anorexia	Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALSO CONSIDER: Weight loss.						
Ascites (non-malignant)	Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
REMARK: Ascites (non-malignant) refers to documented non-malignant ascites or unknown etiology, but unlikely malignant, and includes chylous ascites.						
Colitis	Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain, mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
ALSO CONSIDER: Hemorrhage, GI – <i>Select</i> .						
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
ALSO CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – <i>Select</i> .						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (e.g., hemodynamic collapse)	Death
ALSO CONSIDER: Diarrhea; Hypotension; Vomiting.						
Dental: dentures or prosthesis	Dentures	Minimal discomfort, no restriction in activities	Discomfort preventing use in some activities (e.g., eating), but not others (e.g., speaking)	Unable to use dentures or prosthesis at any time	—	—

GASTROINTESTINAL						
Page 2 of 10						
Adverse Event	Short Name	Grade				
		1	2	3	4	5
Dental: periodontal disease	Periodontal	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	—	—
REMARK: Severe periodontal disease leading to osteonecrosis is graded as Osteonecrosis (avascular necrosis) in the MUSCULOSKELETAL CATEGORY.						
Dental: teeth	Teeth	Surface stains; dental caries; restorable, without extractions	Less than full mouth extractions; tooth fracture or crown amputation or repair indicated	Full mouth extractions indicated	—	—
Dental: teeth development	Teeth development	Hypoplasia of tooth or enamel not interfering with function	Functional impairment correctable with oral surgery	Maldevelopment with functional impairment not surgically correctable	—	—
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea.						
ALSO CONSIDER: Dehydration; Hypotension.						
Distension/bloating, abdominal	Distension	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic, interfering with GI function	—	—
ALSO CONSIDER: Ascites (non-malignant); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – <i>Select</i> .						

GASTROINTESTINAL							Page 3 of 10
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Dry mouth/salivary gland (xerostomia)	Dry mouth	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	—	—	
REMARK: Dry mouth/salivary gland (xerostomia) includes descriptions of grade using both subjective and objective assessment parameters. Record this event consistently throughout a patient's participation on study. If salivary flow measurements are used for initial assessment, subsequent assessments must use salivary flow. ALSO CONSIDER: Salivary gland changes/saliva.							
Dysphagia (difficulty swallowing)	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death	
REMARK: Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilation is graded as Stricture/stenosis (including anastomotic), GI – Select. ALSO CONSIDER: Dehydration; Esophagitis.							
Enteritis (inflammation of the small bowel)	Enteritis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death	
ALSO CONSIDER: Hemorrhage, GI – Select; Typhlitis (cecal inflammation).							
Esophagitis	Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death	
REMARK: Esophagitis includes reflux esophagitis. ALSO CONSIDER: Dysphagia (difficulty swallowing).							

GASTROINTESTINAL							Page 4 of 10
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Fistula, GI – Select: – Abdomen NOS – Anus – Biliary tree – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Oral cavity – Pancreas – Pharynx – Rectum – Salivary gland – Small bowel NOS – Stomach	Fistula, GI – Select	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death	
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer is graded as Fistula, GI – esophagus.							
Flatulence	Flatulence	Mild	Moderate	—	—	—	
Gastritis (including bile reflux gastritis)	Gastritis	Asymptomatic radiographic or endoscopic findings only	Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs	Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., gastrectomy)	Death	
ALSO CONSIDER: Hemorrhage, GI – Select; Ulcer, GI – Select.							
NAVIGATION NOTE: Head and neck soft tissue necrosis is graded as Soft tissue necrosis – Select in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.							
Heartburn/dyspepsia	Heartburn	Mild	Moderate	Severe	—	—	
Hemorrhoids	Hemorrhoids	Asymptomatic	Symptomatic; banding or medical intervention indicated	Interfering with ADL; interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death	

GASTROINTESTINAL						
Page 5 of 10						
Adverse Event	Short Name	Grade				
		1	2	3	4	5
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Ileus	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Ileus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying). ALSO CONSIDER: Constipation; Nausea; Obstruction, GI – <i>Select</i> ; Vomiting.						
Incontinence, anal	Incontinence, anal	Occasional use of pads required	Daily use of pads required	Interfering with ADL; operative intervention indicated	Permanent bowel diversion indicated	Death
REMARK: Incontinence, anal is to be used for loss of sphincter control as sequelae of operative or therapeutic intervention.						
Leak (including anastomotic), GI – <i>Select</i> : – Biliary tree – Esophagus – Large bowel – Leak NOS – Pancreas – Pharynx – Rectum – Small bowel – Stoma – Stomach	Leak, GI – <i>Select</i>	Asymptomatic radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interfering with GI function; invasive or endoscopic intervention indicated	Life-threatening consequences	Death
REMARK: Leak (including anastomotic), GI – <i>Select</i> is to be used for clinical signs/symptoms or radiographic confirmation of anastomotic or conduit leak (e.g., biliary, esophageal, intestinal, pancreatic, pharyngeal, rectal), but without development of fistula.						
Malabsorption	Malabsorption	—	Altered diet; oral therapies indicated (e.g., enzymes, medications, dietary supplements)	Inability to aliment adequately via GI tract (i.e., TPN indicated)	Life-threatening consequences	Death

GASTROINTESTINAL						
Page 6 of 10						
Adverse Event	Short Name	Grade				
		1	2	3	4	5
Mucositis/stomatitis (clinical exam) – Select: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (clinical exam) – Select	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
REMARK: Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.						
Mucositis/stomatitis (functional/symptomatic) – Select: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (functional/symptomatic) – Select	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Anorexia; Vomiting.						

GASTROINTESTINAL						
Page 7 of 10						
Adverse Event	Short Name	Grade				
		1	2	3	4	5
Necrosis, GI – Select: – Anus – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Hepatic – Ileum – Jejunum – Oral – Pancreas – Peritoneal cavity – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Necrosis, GI – Select	—	—	Inability to aliment adequately by GI tract (e.g., requiring enteral or parenteral nutrition); interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
ALSO CONSIDER: Visceral arterial ischemia (non-myocardial).						
Obstruction, GI – Select: – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Obstruction, GI – Select	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – Select Organ or Structure in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
NAVIGATION NOTE: Pelvic pain is graded as Pain – Select in the PAIN CATEGORY.						

GASTROINTESTINAL						
Page 8 of 10						
Adverse Event	Short Name	Grade				
		1	2	3	4	5
Perforation, GI – Select: – Appendix – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stomach	Perforation, GI – Select	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated <24 hrs	IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences	Death
Proctitis	Proctitis	Rectal discomfort, intervention not indicated	Symptoms not interfering with ADL; medical intervention indicated	Stool incontinence or other symptoms interfering with ADL; operative intervention indicated	Life-threatening consequences (e.g., perforation)	Death
Prolapse of stoma, GI	Prolapse of stoma, GI	Asymptomatic	Extraordinary local care or maintenance; minor revision indicated	Dysfunctional stoma; major revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GI – Select; Leak (including anastomotic), GI – Select; Obstruction, GI – Select; Perforation, GI – Select; Stricture/stenosis (including anastomotic), GI – Select.						
NAVIGATION NOTE: Rectal or perirectal pain (proctalgia) is graded as Pain – Select in the PAIN CATEGORY.						
Salivary gland changes/saliva	Salivary gland changes	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms not interfering with ADL	Acute salivary gland necrosis; severe secretion-induced symptoms interfering with ADL	Disabling	—
ALSO CONSIDER: Dry mouth/salivary gland (xerostomia); Mucositis/stomatitis (clinical exam) – Select; Mucositis/stomatitis (functional/symptomatic) – Select; Taste alteration (dysgeusia).						
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						

GASTROINTESTINAL						
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Adverse Event	Short Name	Grade				
		1	2	3	4	5
Stricture/stenosis (including anastomotic), GI – Select: – Anus – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Pancreas/pancreatic duct – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Stricture, GI – Select	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Taste alteration (dysgeusia)	Taste alteration	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	—	—	—
Typhlitis (cecal inflammation)	Typhlitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis); operative intervention indicated	Death
ALSO CONSIDER: Colitis; Hemorrhage, GI – Select; Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation).						

GASTROINTESTINAL						
Page 10 of 10						
Adverse Event	Short Name	Grade				
		1	2	3	4	5
Ulcer, GI – Select: – Anus – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Ulcer, GI – Select	Asymptomatic, radiographic or endoscopic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Hemorrhage, GI – Select.						
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Dehydration.						
Gastrointestinal – Other (Specify, __)	GI – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GROWTH AND DEVELOPMENT						
Page 1 of 1						
Adverse Event	Short Name	Grade				
		1	2	3	4	5
Bone age (alteration in bone age)	Bone age	—	±2 SD (standard deviation) from normal	—	—	—
Bone growth: femoral head; slipped capital femoral epiphysis	Femoral head growth	Mild valgus/varus deformity	Moderate valgus/varus deformity, symptomatic, interfering with function but not interfering with ADL	Mild slipped capital femoral epiphysis; operative intervention (e.g., fixation) indicated; interfering with ADL	Disabling; severe slipped capital femoral epiphysis >60%; avascular necrosis	—
Bone growth: limb length discrepancy	Limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 – 5 cm; shoe lift indicated	Severe length discrepancy >5 cm; operative intervention indicated; interfering with ADL	Disabling; epiphysiodesis	—
Bone growth: spine kyphosis/lordosis	Kyphosis/lordosis	Mild radiographic changes	Moderate accentuation; interfering with function but not interfering with ADL	Severe accentuation; operative intervention indicated; interfering with ADL	Disabling (e.g., cannot lift head)	—
Growth velocity (reduction in growth velocity)	Reduction in growth velocity	10 – 29% reduction in growth from the baseline growth curve	30 – 49% reduction in growth from the baseline growth curve	≥50% reduction in growth from the baseline growth curve	—	—
Puberty (delayed)	Delayed puberty	—	No breast development by age 13 yrs for females; no Tanner Stage 2 development by age 14.5 yrs for males	No sexual development by age 14 yrs for girls; age 16 yrs for boys; hormone replacement indicated	—	—
REMARK: Do not use testicular size for Tanner Stage in male cancer survivors.						
Puberty (precocious)	Precocious puberty	—	Physical signs of puberty <7 years for females, <9 years for males	—	—	—
Short stature	Short stature	Beyond two standard deviations of age and gender mean height	Altered ADL	—	—	—
REMARK: Short stature is secondary to growth hormone deficiency. ALSO CONSIDER: Neuroendocrine: growth hormone secretion abnormality.						
Growth and Development – Other (Specify, __)	Growth and Development – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

HEMORRHAGE/BLEEDING						Page 1 of 4
Adverse Event	Short Name	Grade				
		1	2	3	4	5
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Hematoma refers to extravasation at wound or operative site or secondary to other intervention. Transfusion implies pRBC.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage/bleeding associated with surgery, intra-operative or postoperative	Hemorrhage with surgery	—	—	Requiring transfusion of 2 units non-autologous (10 cc/kg for pediatrics) pRBCs beyond protocol specification, postoperative interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death
REMARK: Postoperative period is defined as ≤72 hours after surgery. Verify protocol-specific acceptable guidelines regarding pRBC transfusion.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, CNS	CNS hemorrhage	Asymptomatic, radiographic findings only	Medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; neurologic deficit or disability	Death
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING						Page 2 of 4
Adverse Event	Short Name	Grade				
		1	2	3	4	5
Hemorrhage, GI – Select: – Abdomen NOS – Anus – Biliary tree – Cecum/appendix – Colon – Duodenum – Esophagus – Ileum – Jejunum – Liver – Lower GI NOS – Oral cavity – Pancreas – Peritoneal cavity – Rectum – Stoma – Stomach – Upper GI NOS – Varices (esophageal) – Varices (rectal)	Hemorrhage, GI – Select	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING							Page 3 of 4
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
Hemorrhage, GU – Select: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Retroperitoneum – Spermatic cord – Stoma – Testes – Ureter – Urethra – Urinary NOS – Uterus – Vagina – Vas deferens	Hemorrhage, GU – Select	Minimal or microscopic bleeding; intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death	
REMARK: Transfusion implies pRBC.							
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).							
Hemorrhage, pulmonary/upper respiratory – Select: – Bronchopulmonary NOS – Bronchus – Larynx – Lung – Mediastinum – Nose – Pharynx – Pleura – Respiratory tract NOS – Stoma – Trachea	Hemorrhage pulmonary – Select	Mild, intervention not indicated	Symptomatic and medical intervention indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death	
REMARK: Transfusion implies pRBC.							
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).							
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	Petechiae	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura	—	—	
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).							

HEMORRHAGE/BLEEDING							Page 4 of 4
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
NAVIGATION NOTE: Vitreous hemorrhage is graded in the OCULAR/VISUAL CATEGORY.							
Hemorrhage/Bleeding – Other (Specify, __)	Hemorrhage – Other (Specify)	Mild without transfusion	—	Transfusion indicated	Catastrophic bleeding, requiring major non-elective intervention	Death	

HEPATOBIILIARY/PANCREAS							Page 1 of 1
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
NAVIGATION NOTE: Biliary tree damage is graded as Fistula, GI – Select; Leak (including anastomotic), GI – Select; Necrosis, GI – Select; Obstruction, GI – Select; Perforation, GI – Select; Stricture/stenosis (including anastomotic), GI – Select in the GASTROINTESTINAL CATEGORY.							
Cholecystitis	Cholecystitis	Asymptomatic, radiographic findings only	Symptomatic, medical intervention indicated	Interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)	Death	
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils – Select; Infection with normal ANC or Grade 1 or 2 neutrophils – Select; Infection with unknown ANC – Select.							
Liver dysfunction/failure (clinical)	Liver dysfunction	—	Jaundice	Asterixis	Encephalopathy or coma	Death	
REMARK: Jaundice is not an AE, but occurs when the liver is not working properly or when a bile duct is blocked. It is graded as a result of liver dysfunction/failure or elevated bilirubin.							
ALSO CONSIDER: Bilirubin (hyperbilirubinemia).							
Pancreas, exocrine enzyme deficiency	Pancreas, exocrine enzyme deficiency	—	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency (e.g., weight loss)	Life-threatening consequences	Death	
ALSO CONSIDER: Diarrhea.							
Pancreatitis	Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)	Death	
ALSO CONSIDER: Amylase.							
NAVIGATION NOTE: Stricture (biliary tree, hepatic or pancreatic) is graded as Stricture/stenosis (including anastomotic), GI – Select in the GASTROINTESTINAL CATEGORY.							
Hepatobiliary/Pancreas – Other (Specify, __)	Hepatobiliary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death	

INFECTION							Page 1 of 3
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
Colitis, infectious (e.g., Clostridium difficile)	Colitis, infectious	Asymptomatic, pathologic or radiographic findings only	Abdominal pain with mucus and/or blood in stool	IV antibiotics or TPN indicated	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis or toxic megacolon); operative resection or diversion indicated	Death	
ALSO CONSIDER: Hemorrhage, GI – <i>Select</i> ; Typhitis (cecal inflammation).							
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10 ⁹ /L, fever ≥38.5°C)	Febrile neutropenia	—	—	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death	
ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).							
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10 ⁹ /L) – <i>Select</i>	Infection (documented clinically) – <i>Select</i>	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death	
‘ <i>Select</i> ’ AEs appear at the end of the CATEGORY.							
REMARK: Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection).							
ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).							
Infection with normal ANC or Grade 1 or 2 neutrophils – <i>Select</i>	Infection with normal ANC – <i>Select</i>	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death	
‘ <i>Select</i> ’ AEs appear at the end of the CATEGORY.							

INFECTION							Page 2 of 3
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
Infection with unknown ANC – <i>Select</i>	Infection with unknown ANC – <i>Select</i>	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death	
‘ <i>Select</i> ’ AEs appear at the end of the CATEGORY.							
REMARK: Infection with unknown ANC – <i>Select</i> is to be used in the rare case when ANC is unknown.							
Opportunistic infection associated with ≥Grade 2 Lymphopenia	Opportunistic infection	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death	
ALSO CONSIDER: Lymphopenia.							
Viral hepatitis	Viral hepatitis	Present; transaminases and liver function normal	Transaminases abnormal, liver function normal	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death	
REMARK: Non-viral hepatitis is graded as Infection – <i>Select</i> .							
ALSO CONSIDER: Albumin, serum-low (hypoalbuminemia); ALT, SGPT (serum glutamic pyruvic transaminase); AST, SGOT (serum glutamic oxaloacetic transaminase); Bilirubin (hyperbilirubinemia); Encephalopathy.							
Infection – Other (Specify, __)	Infection – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death	

INFECTION – SELECT			Page 3 of 3
AUDITORY/EAR – External ear (otitis externa) – Middle ear (otitis media) CARDIOVASCULAR – Artery – Heart (endocarditis) – Spleen – Vein DERMATOLOGY/SKIN – Lip/perioral – Peristomal – Skin (cellulitis) – Ungual (nails) GASTROINTESTINAL – Abdomen NOS – Anal/perianal – Appendix – Cecum – Colon – Dental-tooth – Duodenum – Esophagus – Ileum – Jejunum – Oral cavity-gums (gingivitis) – Peritoneal cavity – Rectum – Salivary gland – Small bowel NOS – Stomach	GENERAL – Blood – Catheter-related – Foreign body (e.g., graft, implant, prosthesis, stent) – Wound HEPATOBIILIARY/PANCREAS – Biliary tree – Gallbladder (cholecystitis) – Liver – Pancreas LYMPHATIC – Lymphatic MUSCULOSKELETAL – Bone (osteomyelitis) – Joint – Muscle (infection myositis) – Soft tissue NOS NEUROLOGY – Brain (encephalitis, infectious) – Brain + Spinal cord (encephalomyelitis) – Meninges (meningitis) – Nerve-cranial – Nerve-peripheral – Spinal cord (myelitis) OCULAR – Conjunctiva – Cornea – Eye NOS – Lens	PULMONARY/UPPER RESPIRATORY – Bronchus – Larynx – Lung (pneumonia) – Mediastinum NOS – Mucosa – Neck NOS – Nose – Paranasal – Pharynx – Pleura (empyema) – Sinus – Trachea – Upper aerodigestive NOS – Upper airway NOS RENAL/GENITOURINARY – Bladder (urinary) – Kidney – Prostate – Ureter – Urethra – Urinary tract NOS SEXUAL/REPRODUCTIVE FUNCTION – Cervix – Fallopian tube – Pelvis NOS – Penis – Scrotum – Uterus – Vagina – Vulva	

LYMPHATICS							Page 1 of 2
Adverse Event		Short Name		Grade			
		1	2	3	4	5	
Chyle or lymph leakage	Chyle or lymph leakage	Asymptomatic, clinical or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening complications	Death	
ALSO CONSIDER: Chylothorax.							
Dermal change lymphedema, phlebolympheidema	Dermal change	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation	—	—	—	
REMARK: Dermal change lymphedema, phlebolympheidema refers to changes due to venous stasis.							
ALSO CONSIDER: Ulceration.							
Edema: head and neck	Edema: head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death	
Edema: limb	Edema: limb	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death	
Edema: trunk/genital	Edema: trunk/genital	Swelling or obscuration of anatomic architecture on close inspection; pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL; gross deviation from normal anatomic contour	Progression to malignancy (i.e., lymphangiosarcoma); disabling	Death	
Edema: viscera	Edema: viscera	Asymptomatic; clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and unable to aliment adequately orally; interventional radiology or operative intervention indicated	Life-threatening consequences	Death	

LYMPHATICS							Page 2 of 2
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
Lymphedema-related fibrosis	Lymphedema-related fibrosis	Minimal to moderate redundant soft tissue, unresponsive to elevation or compression, with moderately firm texture or spongy feel	Marked increase in density and firmness, with or without tethering	Very marked density and firmness with tethering affecting >40% of the edematous area	—	—	
Lymphocele	Lymphocele	Asymptomatic, clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interventional radiology or operative intervention indicated	—	—	
Phlebolympathic cording	Phlebolympathic cording	Asymptomatic, clinical findings only	Symptomatic; medical intervention indicated	Symptomatic and leading to contracture or reduced range of motion	—	—	
Lymphatics – Other (Specify, ___)	Lymphatics – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death	

METABOLIC/LABORATORY							Page 1 of 3
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
Acidosis (metabolic or respiratory)	Acidosis	pH <normal, but ≥ 7.3	—	pH <7.3	pH <7.3 with life-threatening consequences	Death	
Albumin, serum-low (hypoalbuminemia)	Hypoalbuminemia	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	—	Death	
Alkaline phosphatase	Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—	
Alkalosis (metabolic or respiratory)	Alkalosis	pH >normal, but ≤ 7.5	—	pH >7.5	pH >7.5 with life-threatening consequences	Death	
ALT, SGPT (serum glutamic pyruvic transaminase)	ALT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—	
Amylase	Amylase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—	
AST, SGOT (serum glutamic oxaloacetic transaminase)	AST	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—	
Bicarbonate, serum-low	Bicarbonate, serum-low	<LLN – 16 mmol/L	<16 – 11 mmol/L	<11 – 8 mmol/L	<8 mmol/L	Death	
Bilirubin (hyperbilirubinemia)	Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	—	
REMARK: Jaundice is not an AE, but may be a manifestation of liver dysfunction/failure or elevated bilirubin. If jaundice is associated with elevated bilirubin, grade bilirubin.							
Calcium, serum-low (hypocalcemia)	Hypocalcemia	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium: <LLN – 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium: <1.0 – 0.9 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium: <0.9 – 0.8 mmol/L	<6.0 mg/dL <1.5 mmol/L Ionized calcium: <0.8 mmol/L	Death	
REMARK: Calcium can be falsely low if hypoalbuminemia is present. Serum albumin is <4.0 g/dL, hypocalcemia is reported after the following corrective calculation has been performed: Corrected Calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) – 4] ⁴ . Alternatively, direct measurement of ionized calcium is the definitive method to diagnose metabolically relevant alterations in serum calcium.							

METABOLIC/LABORATORY						Page 2 of 3
Adverse Event	Short Name	Grade				
		1	2	3	4	5
Calcium, serum-high (hypercalcemia)	Hypercalcemia	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium: >ULN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium: >1.5 – 1.6 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium: >1.6 – 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L Ionized calcium: >1.8 mmol/L	Death
Cholesterol, serum-high (hypercholesteremia)	Cholesterol	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L	Death
CPK (creatine phosphokinase)	CPK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	Death
Creatinine	Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death
REMARK: Adjust to age-appropriate levels for pediatric patients. ALSO CONSIDER: Glomerular filtration rate.						
GGT (γ-Glutamyl transpeptidase)	GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Glomerular filtration rate	GFR	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Creatinine.						
Glucose, serum-high (hyperglycemia)	Hyperglycemia	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis	Death
REMARK: Hyperglycemia, in general, is defined as fasting unless otherwise specified in protocol.						
Glucose, serum-low (hypoglycemia)	Hypoglycemia	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L	Death
Hemoglobinuria	Hemoglobinuria	Present	—	—	—	Death
Lipase	Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
Magnesium, serum-high (hypermagnesemia)	Hypermagnesemia	>ULN – 3.0 mg/dL >ULN – 1.23 mmol/L	—	>3.0 – 8.0 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L	Death
Magnesium, serum-low (hypomagnesemia)	Hypomagnesemia	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L	Death
Phosphate, serum-low (hypophosphatemia)	Hypophosphatemia	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L	Death
Potassium, serum-high (hyperkalemia)	Hyperkalemia	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	Death

METABOLIC/LABORATORY						Page 3 of 3
Adverse Event	Short Name	Grade				
		1	2	3	4	5
Potassium, serum-low (hypokalemia)	Hypokalemia	<LLN – 3.0 mmol/L	—	<3.0 – 2.5 mmol/L	<2.5 mmol/L	Death
Proteinuria	Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome	Death
Sodium, serum-high (hypernatremia)	Hypernatremia	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	Death
Sodium, serum-low (hyponatremia)	Hyponatremia	<LLN – 130 mmol/L	—	<130 – 120 mmol/L	<120 mmol/L	Death
Triglyceride, serum-high (hypertriglyceridemia)	Hypertriglyceridemia	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN	Death
Uric acid, serum-high (hyperuricemia)	Hyperuricemia	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	—	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia); Renal failure; Tumor lysis syndrome.						
Metabolic/Laboratory – Other (Specify, ___)	Metabolic/Lab – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

MUSCULOSKELETAL/SOFT TISSUE						
Page 1 of 4						
Adverse Event	Short Name	Grade				
		1	2	3	4	5
Arthritis (non-septic)	Arthritis	Mild pain with inflammation, erythema, or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with ADL	Severe pain with inflammation, erythema, or joint swelling and interfering with ADL	Disabling	Death
REMARK: Report only when the diagnosis of arthritis (e.g., inflammation of a joint or a state characterized by inflammation of joints) is made. Arthralgia (sign or symptom of pain in a joint, especially non-inflammatory in character) is graded as Pain – Select in the PAIN CATEGORY.						
Bone: spine-scoliosis	Scoliosis	≤20 degrees; clinically undetectable	>20 – 45 degrees; visible by forward flexion; interfering with function but not interfering with ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; interfering with ADL	Disabling (e.g., interfering with cardiopulmonary function)	Death
Cervical spine-range of motion	Cervical spine ROM	Mild restriction of rotation or flexion between 60 – 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	—	—
REMARK: 60 – 65 degrees of rotation is required for reversing a car; 60 – 65 degrees of flexion is required to tie shoes.						
Exostosis	Exostosis	Asymptomatic	Involving multiple sites; pain or interfering with function	Excision indicated	Progression to malignancy (i.e., chondrosarcoma)	Death
Extremity-lower (gait/walking)	Gait/walking	Limp evident only to trained observer and able to walk ≥1 kilometer; cane indicated for walking	Noticeable limp, or limitation of limb function, but able to walk ≥0.1 kilometer (1 city block); quad cane indicated for walking	Severe limp with stride modified to maintain balance (widened base of support, marked reduction in step length); ambulation limited to walker; crutches indicated	Unable to walk	—
ALSO CONSIDER: Ataxia (incoordination); Muscle weakness, generalized or specific area (not due to neuropathy) – Select.						
Extremity-upper (function)	Extremity-upper (function)	Able to perform most household or work activities with affected limb	Able to perform most household or work activities with compensation from unaffected limb	Interfering with ADL	Disabling; no function of affected limb	—
Fibrosis-cosmesis	Fibrosis-cosmesis	Visible only on close examination	Readily apparent but not disfiguring	Significant disfigurement; operative intervention indicated if patient chooses	—	—

MUSCULOSKELETAL/SOFT TISSUE						
Page 2 of 4						
Adverse Event	Short Name	Grade				
		1	2	3	4	5
Fibrosis-deep connective tissue	Fibrosis-deep connective tissue	Increased density, "spongy" feel	Increased density with firmness or tethering	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL	Life-threatening; disabling; loss of limb; interfering with vital organ function	Death
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue); Muscle weakness, generalized or specific area (not due to neuropathy) – Select; Neuropathy: motor; Neuropathy: sensory.						
Fracture	Fracture	Asymptomatic, radiographic findings only (e.g., asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on MRI, etc.)	Symptomatic but non-displaced; immobilization indicated	Symptomatic and displaced or open wound with bone exposure; operative intervention indicated	Disabling; amputation indicated	Death
Joint-effusion	Joint-effusion	Asymptomatic, clinical or radiographic findings only	Symptomatic; interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death
ALSO CONSIDER: Arthritis (non-septic).						
Joint-function ⁵	Joint-function	Stiffness interfering with athletic activity; <25% loss of range of motion (ROM)	Stiffness interfering with function but not interfering with ADL; >25 – 50% decrease in ROM	Stiffness interfering with ADL; >50 – 75% decrease in ROM	Fixed or non-functional joint (arthrodesis); >75% decrease in ROM	—
ALSO CONSIDER: Arthritis (non-septic).						
Local complication – device/prosthesis-related	Device/prosthesis	Asymptomatic	Symptomatic, but not interfering with ADL; local wound care; medical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated (e.g., hardware/device replacement or removal, reconstruction)	Life-threatening; disabling; loss of limb or organ	Death
Lumbar spine-range of motion	Lumbar spine ROM	Stiffness and difficulty bending to the floor to pick up a very light object but able to do activity	Some lumbar spine flexion but requires a reaching aid to pick up a very light object from the floor	Ankylosed/fused over multiple segments with no L-spine flexion (i.e., unable to reach to floor to pick up a very light	—	—

MUSCULOSKELETAL/SOFT TISSUE						Page 3 of 4
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Muscle weakness, generalized or specific area (not due to neuropathy) – <i>Select</i> : – Extraocular – Extremity-lower – Extremity-upper – Facial – Left-sided – Ocular – Pelvic – Right-sided – Trunk – Whole body/generalized	Muscle weakness – <i>Select</i>	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Life-threatening; disabling	Death
ALSO CONSIDER: Fatigue (asthenia, lethargy, malaise).						
Muscular/skeletal hypoplasia	Muscular/skeletal hypoplasia	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Functionally significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing	Disabling	—
Myositis (inflammation/damage of muscle)	Myositis	Mild pain, not interfering with function	Pain interfering with function, but not interfering with ADL	Pain interfering with ADL	Disabling	Death
REMARK: Myositis implies muscle damage (i.e., elevated CPK). ALSO CONSIDER: CPK (creatine phosphokinase); Pain – <i>Select</i> .						
Osteonecrosis (avascular necrosis)	Osteonecrosis	Asymptomatic, radiographic findings only	Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (i.e., minor sequestrectomy)	Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indicated	Disabling	Death

MUSCULOSKELETAL/SOFT TISSUE						Page 4 of 4
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Osteoporosis ⁶	Osteoporosis	Radiographic evidence of osteoporosis or Bone Mineral Density (BMD) t-score –1 to –2.5 (osteopenia) and no loss of height or therapy indicated	BMD t-score < –2.5; loss of height <2 cm; anti-osteoporotic therapy indicated	Fractures; loss of height ≥2 cm	Disabling	Death
Seroma	Seroma	Asymptomatic	Symptomatic; medical intervention or simple aspiration indicated	Symptomatic, interventional radiology or operative intervention indicated	—	—
Soft tissue necrosis – <i>Select</i> : – Abdomen – Extremity-lower – Extremity-upper – Head – Neck – Pelvic – Thorax	Soft tissue necrosis – <i>Select</i>	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
Trismus (difficulty, restriction or pain when opening mouth)	Trismus	Decreased range of motion without impaired eating	Decreased range of motion requiring small bites, soft foods or purees	Decreased range of motion with inability to adequately aliment or hydrate orally	—	—
NAVIGATION NOTE: Wound-infectious is graded as Infection – <i>Select</i> in the INFECTION CATEGORY.						
NAVIGATION NOTE: Wound non-infectious is graded as Wound complication, non-infectious in the DERMATOLOGY/SKIN CATEGORY.						
Musculoskeletal/Soft Tissue – Other (Specify, __)	Musculoskeletal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

NEUROLOGY						
Page 1 of 5						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
NAVIGATION NOTE: ADD (Attention Deficit Disorder) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Aphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Apnea	Apnea	—	—	Present	Intubation indicated	Death
Arachnoiditis/meningismus/radiculitis	Arachnoiditis	Symptomatic, not interfering with function; medical intervention indicated	Symptomatic (e.g., photophobia, nausea) interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling (e.g., paraplegia)	Death
ALSO CONSIDER: Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10 ⁹ /L); Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10 ⁹ /L) – <i>Select</i> ; Infection with normal ANC or Grade 1 or 2 neutrophils – <i>Select</i> ; Infection with unknown ANC – <i>Select</i> ; Pain – <i>Select</i> ; Vomiting.						
Ataxia (incoordination)	Ataxia	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; mechanical assistance indicated	Disabling	Death
REMARK: Ataxia (incoordination) refers to the consequence of medical or operative intervention.						
Brachial plexopathy	Brachial plexopathy	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Disabling	Death
CNS cerebrovascular ischemia	CNS ischemia	—	Asymptomatic, radiographic findings only	Transient ischemic event or attack (TIA) ≤24 hrs duration	Cerebral vascular accident (CVA, stroke), neurologic deficit >24 hrs	Death
NAVIGATION NOTE: CNS hemorrhage/bleeding is graded as Hemorrhage, CNS in the HEMORRHAGE/BLEEDING CATEGORY.						
CNS necrosis/cystic progression	CNS necrosis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL; medical intervention indicated	Symptomatic and interfering with ADL; hyperbaric oxygen indicated	Life-threatening; disabling; operative intervention indicated to prevent or treat CNS necrosis/cystic progression	Death
Cognitive disturbance	Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	Unable to perform ADL; full-time specialized resources or institutionalization indicated	Death
REMARK: Cognitive disturbance may be used for Attention Deficit Disorder (ADD).						

NEUROLOGY						
Page 2 of 5						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Confusion	Confusion	Transient confusion, disorientation, or attention deficit	Confusion, disorientation, or attention deficit interfering with function, but not interfering with ADL	Confusion or delirium interfering with ADL	Harmful to others or self; hospitalization indicated	Death
REMARK: Attention Deficit Disorder (ADD) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Cranial neuropathy is graded as Neuropathy-cranial – <i>Select</i> .						
Dizziness	Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabling	—
REMARK: Dizziness includes disequilibrium, lightheadedness, and vertigo.						
ALSO CONSIDER: Neuropathy: cranial – <i>Select</i> ; Syncope (fainting).						
NAVIGATION NOTE: Dysphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Encephalopathy	Encephalopathy	—	Mild signs or symptoms; not interfering with ADL	Signs or symptoms interfering with ADL; hospitalization indicated	Life-threatening; disabling	Death
ALSO CONSIDER: Cognitive disturbance; Confusion; Dizziness; Memory impairment; Mental status; Mood alteration – <i>Select</i> ; Psychosis (hallucinations/delusions); Somnolence/depressed level of consciousness.						
Extrapyramidal/involuntary movement/restlessness	Involuntary movement	Mild involuntary movements not interfering with function	Moderate involuntary movements interfering with function, but not interfering with ADL	Severe involuntary movements or torticollis interfering with ADL	Disabling	Death
NAVIGATION NOTE: Headache/neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies) is graded as Pain – <i>Select</i> in the PAIN CATEGORY.						
Hydrocephalus	Hydrocephalus	Asymptomatic, radiographic findings only	Mild to moderate symptoms not interfering with ADL	Severe symptoms or neurological deficit interfering with ADL	Disabling	Death
Irritability (children <3 years of age)	Irritability	Mild; easily consolable	Moderate; requiring increased attention	Severe; inconsolable	—	—
Laryngeal nerve dysfunction	Laryngeal nerve	Asymptomatic, weakness on clinical examination/testing only	Symptomatic, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening; tracheostomy indicated	Death

NEUROLOGY						
Page 3 of 5						
Adverse Event	Short Name	Grade				
		1	2	3	4	5
Leak, cerebrospinal fluid (CSF)	CSF leak	Transient headache; postural care indicated	Symptomatic, not interfering with ADL; blood patch indicated	Symptomatic, interfering with ADL; operative intervention indicated	Life-threatening; disabling	Death
REMARK: Leak, cerebrospinal fluid (CSF) may be used for CSF leak associated with operation and persisting >72 hours.						
Leukoencephalopathy (radiographic findings)	Leukoencephalopathy	Mild increase in subarachnoid space (SAS); mild ventriculomegaly; small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	Moderate increase in SAS; moderate ventriculomegaly; focal T2 hyperintensities extending into centrum ovale or involving 1/3 to 2/3 of susceptible areas of cerebrum	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT)	—	—
REMARK: Leukoencephalopathy is a diffuse white matter process, specifically NOT associated with necrosis. Leukoencephalopathy (radiographic findings) does not include lacunas, which are areas that become void of neural tissue.						
Memory impairment	Memory impairment	Memory impairment not interfering with function	Memory impairment interfering with function, but not interfering with ADL	Memory impairment interfering with ADL	Amnesia	—
Mental status ⁷	Mental status	—	1 – 3 point below age and educational norm in Folstein Mini-Mental Status Exam (MMSE)	>3 point below age and educational norm in Folstein MMSE	—	—
Mood alteration – Select: – Agitation – Anxiety – Depression – Euphoria	Mood alteration – Select	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or others	Death
Myelitis	Myelitis	Asymptomatic, mild signs (e.g., Babinski's or Lhermitte's sign)	Weakness or sensory loss not interfering with ADL	Weakness or sensory loss interfering with ADL	Disabling	Death
NAVIGATION NOTE: Neuropathic pain is graded as Pain – Select in the PAIN CATEGORY.						

NEUROLOGY						
Page 4 of 5						
Adverse Event	Short Name	Grade				
		1	2	3	4	5
Neuropathy: cranial – Select: – CN I Smell – CN II Vision – CN III Pupil, upper eyelid, extra ocular movements – CN IV Downward, inward movement of eye – CN V Motor-jaw muscles; Sensory-facial – CN VI Lateral deviation of eye – CN VII Motor-face; Sensory-taste – CN VIII Hearing and balance – CN IX Motor-pharynx; Sensory-ear, pharynx, tongue – CN X Motor-palate; pharynx, larynx – CN XI Motor-sternomastoid and trapezius – CN XII Motor-tongue	Neuropathy: cranial – Select	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling	Death
Neuropathy: motor	Neuropathy-motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death
REMARK: Cranial nerve <u>motor</u> neuropathy is graded as Neuropathy: cranial – Select. ALSO CONSIDER: Laryngeal nerve dysfunction; Phrenic nerve dysfunction.						
Neuropathy: sensory	Neuropathy-sensory	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
REMARK: Cranial nerve <u>sensory</u> neuropathy is graded as Neuropathy: cranial – Select.						
Personality/behavioral	Personality	Change, but not adversely affecting patient or family	Change, adversely affecting patient or family	Mental health intervention indicated	Change harmful to others or self; hospitalization indicated	Death
Phrenic nerve dysfunction	Phrenic nerve	Asymptomatic weakness on exam/testing only	Symptomatic but not interfering with ADL; intervention not indicated	Significant dysfunction; intervention indicated (e.g., diaphragmatic plication)	Life-threatening respiratory compromise; mechanical ventilation indicated	Death
Psychosis (hallucinations/delusions)	Psychosis	—	Transient episode	Interfering with ADL; medication, supervision or restraints indicated	Harmful to others or self; life-threatening consequences	Death

NEUROLOGY							Page 5 of 5
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	Pyramidal tract dysfunction	Asymptomatic, abnormality on exam or testing only	Symptomatic; interfering with function but not interfering with ADL	Interfering with ADL	Disabling; paralysis	Death	
Seizure	Seizure	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death	
Somnolence/depressed level of consciousness	Somnolence	—	Somnolence or sedation interfering with function, but not interfering with ADL	Obtundation or stupor; difficult to arouse; interfering with ADL	Coma	Death	
Speech impairment (e.g., dysphasia or aphasia)	Speech impairment	—	Awareness of receptive or expressive dysphasia, not impairing ability to communicate	Receptive or expressive dysphasia, impairing ability to communicate	Inability to communicate	—	
REMARK: Speech impairment refers to a primary CNS process, not neuropathy or end organ dysfunction. ALSO CONSIDER: Laryngeal nerve dysfunction; Voice changes/dysarthria (e.g., hoarseness, loss, or alteration in voice, laryngitis).							
Syncope (fainting)	Syncope (fainting)	—	—	Present	Life-threatening consequences	Death	
ALSO CONSIDER: CNS cerebrovascular ischemia; Conduction abnormality/atrioventricular heart block – <i>Select</i> ; Dizziness; Supraventricular and nodal arrhythmia – <i>Select</i> ; Vasovagal episode; Ventricular arrhythmia – <i>Select</i> .							
NAVIGATION NOTE: Taste alteration (CN VII, IX) is graded as Taste alteration (dysgeusia) in the GASTROINTESTINAL CATEGORY.							
Tremor	Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADL	Severe tremor interfering with ADL	Disabling	—	
Neurology – Other (Specify, ___)	Neurology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death	

OCULAR/VISUAL							Page 1 of 3
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
Cataract	Cataract	Asymptomatic, detected on exam only	Symptomatic, with moderate decrease in visual acuity (20/40 or better); decreased visual function correctable with glasses	Symptomatic with marked decrease in visual acuity (worse than 20/40); operative intervention indicated (e.g., cataract surgery)	—	—	
Dry eye syndrome	Dry eye	Mild, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL; medical intervention indicated	Symptomatic or decrease in visual acuity interfering with ADL; operative intervention indicated	—	—	
Eyelid dysfunction	Eyelid dysfunction	Asymptomatic	Symptomatic, interfering with function but not ADL; requiring topical agents or epilation	Symptomatic; interfering with ADL; surgical intervention indicated	—	—	
REMARK: Eyelid dysfunction includes canaliculus stenosis, ectropion, entropion, erythema, madarosis, symblepharon, telangiectasis, thickening, and trichiasis. ALSO CONSIDER: Neuropathy: cranial – <i>Select</i> .							
Glaucoma	Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficit (i.e., nasal step or arcuate deficit); multiple topical or oral agents indicated	EIOP causing marked visual field deficits (i.e., involving both superior and inferior visual fields); operative intervention indicated	EIOP resulting in blindness (20/200 or worse); enucleation indicated	—	
Keratitis (corneal inflammation/corneal ulceration)	Keratitis	Abnormal ophthalmologic changes only; intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL; operative intervention indicated	Perforation or blindness (20/200 or worse)	—	
NAVIGATION NOTE: Ocular muscle weakness is graded as Muscle weakness, generalized or specific area (not due to neuropathy) – <i>Select</i> in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.							
Night blindness (nyctalopia)	Nyctalopia	Symptomatic, not interfering with function	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—	

OCULAR/VISUAL							Page 2 of 3
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Nystagmus	Nystagmus	Asymptomatic	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—	
ALSO CONSIDER: Neuropathy: cranial – Select; Ophthalmoplegia/diplopia (double vision).							
Ocular surface disease	Ocular surface disease	Asymptomatic or minimally symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; topical antibiotics or other topical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated	—	—	
REMARK: Ocular surface disease includes conjunctivitis, keratoconjunctivitis sicca, chemosis, keratinization, and palpebral conjunctival epithelial metaplasia.							
Ophthalmoplegia/diplopia (double vision)	Diplopia	Intermittently symptomatic, intervention not indicated	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL; surgical intervention indicated	Disabling	—	
ALSO CONSIDER: Neuropathy: cranial – Select.							
Optic disc edema	Optic disc edema	Asymptomatic	Decreased visual acuity (20/40 or better); visual field defect present	Decreased visual acuity (worse than 20/40); marked visual field defect but sparing the central 20 degrees	Blindness (20/200 or worse)	—	
ALSO CONSIDER: Neuropathy: cranial – Select.							
Proptosis/enophthalmos	Proptosis/enophthalmos	Asymptomatic, intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	—	—	
Retinal detachment	Retinal detachment	Exudative; no central vision loss; intervention not indicated	Exudative and visual acuity 20/40 or better but intervention not indicated	Rhegmatogenous or exudative detachment; operative intervention indicated	Blindness (20/200 or worse)	—	
Retinopathy	Retinopathy	Asymptomatic	Symptomatic with moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse)	—	

OCULAR/VISUAL							Page 3 of 3
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Scleral necrosis/melt	Scleral necrosis	Asymptomatic or symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; moderate decrease in visual acuity (20/40 or better); medical intervention indicated	Symptomatic, interfering with ADL; marked decrease in visual acuity (worse than 20/40); operative intervention indicated	Blindness (20/200 or worse); painful eye with enucleation indicated	—	
Uveitis	Uveitis	Asymptomatic	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis; operative intervention indicated	Blindness (20/200 or worse)	—	
Vision-blurred vision	Blurred vision	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—	
Vision-flashing lights/floaters	Flashing lights	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—	
Vision-photophobia	Photophobia	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—	
Vitreous hemorrhage	Vitreous hemorrhage	Asymptomatic, clinical findings only	Symptomatic, interfering with function, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; vitrectomy indicated	—	—	
Watery eye (epiphora, tearing)	Watery eye	Symptomatic, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	—	—	
Ocular/Visual – Other (Specify, __)	Ocular – Other (Specify)	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Blindness (20/200 or worse)	Death	

PAIN							Page 1 of 1
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Pain – Select: *Select* AEs appear at the end of the CATEGORY.	Pain – Select	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—	
Pain – Other (Specify, ___)	Pain – Other (Specify)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—	
PAIN – SELECT							
AUDITORY/EAR – External ear – Middle ear		HEPATOBIILIARY/PANCREAS – Gallbladder – Liver		PULMONARY/UPPER RESPIRATORY (<i>continued</i>) – Larynx – Pleura – Sinus – Throat/pharynx/larynx			
CARDIOVASCULAR – Cardiac/heart – Pericardium		LYMPHATIC – Lymph node		RENAL/GENITOURINARY – Bladder – Kidney			
DERMATOLOGY/SKIN – Face – Lip – Oral-gums – Scalp – Skin		MUSCULOSKELETAL – Back – Bone – Buttock – Extremity-limb – Intestine – Joint – Muscle – Neck – Phantom (pain associated with missing limb)		SEXUAL/REPRODUCTIVE FUNCTION – Breast – Ovary – Pelvis – Penis – Perineum – Prostate – Scrotum – Testicle – Urethra – Uterus – Vagina			
GASTROINTESTINAL – Abdomen NOS – Anus – Dental/teeth/peridontal – Esophagus – Oral cavity – Peritoneum – Rectum – Stomach		NEUROLOGY – Head/headache – Neuralgia/peripheral nerve					
GENERAL – Pain NOS – Tumor pain		OCULAR – Eye					
		PULMONARY/UPPER RESPIRATORY – Chest wall – Chest/thorax NOS					

PULMONARY/UPPER RESPIRATORY							Page 1 of 4
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Adult Respiratory Distress Syndrome (ARDS)	ARDS	—	—	Present, intubation not indicated	Present, intubation indicated	Death	
ALSO CONSIDER: Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates.							
Aspiration	Aspiration	Asymptomatic ("silent aspiration"); endoscopy or radiographic (e.g., barium swallow) findings	Symptomatic (e.g., altered eating habits, coughing or choking episodes consistent with aspiration); medical intervention indicated (e.g., antibiotics, suction or oxygen)	Clinical or radiographic signs of pneumonia or pneumonitis; unable to aliment orally	Life-threatening (e.g., aspiration pneumonia or pneumonitis)	Death	
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10 ⁹ /L) – Select; Infection with normal ANC or Grade 1 or 2 neutrophils – Select; Infection with unknown ANC – Select; Laryngeal nerve dysfunction; Neuropathy: cranial – Select; Pneumonitis/pulmonary infiltrates.							
Atelectasis	Atelectasis	Asymptomatic	Symptomatic (e.g., dyspnea, cough), medical intervention indicated (e.g., bronchoscopic suctioning, chest physiotherapy, suctioning)	Operative (e.g., stent, laser) intervention indicated	Life-threatening respiratory compromise	Death	
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10 ⁹ /L) – Select; Infection with normal ANC or Grade 1 or 2 neutrophils – Select; Infection with unknown ANC – Select; Obstruction/stenosis of airway – Select; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).							
Bronchospasm, wheezing	Bronchospasm	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death	
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Dyspnea (shortness of breath).							
Carbon monoxide diffusion capacity (DL _{CO})	DL _{CO}	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death	
ALSO CONSIDER: Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).							
Chylothorax	Chylothorax	Asymptomatic	Symptomatic; thoracentesis or tube drainage indicated	Operative intervention indicated	Life-threatening (e.g., hemodynamic instability or ventilatory support indicated)	Death	
Cough	Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	—	—	

PULMONARY/UPPER RESPIRATORY						
Page 2 of 4						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Dyspnea (shortness of breath)	Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1 km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death
ALSO CONSIDER: Hypoxia; Neuropathy: motor; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Edema, larynx	Edema, larynx	Asymptomatic edema by exam only	Symptomatic edema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening airway compromise; tracheotomy, intubation, or laryngectomy indicated	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
FEV ₁	FEV ₁	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted	Death
Fistula, pulmonary/upper respiratory – <i>Select</i> : – Bronchus – Larynx – Lung – Oral cavity – Pharynx – Pleura – Trachea	Fistula, pulmonary – <i>Select</i>	Asymptomatic, radiographic findings only	Symptomatic, tube thoracostomy or medical management indicated; associated with altered respiratory function but not interfering with ADL	Symptomatic and associated with altered respiratory function interfering with ADL; or endoscopic (e.g., stent) or primary closure by operative intervention indicated	Life-threatening consequences; operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have arisen. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer should be graded as Fistula, GI – esophagus in the GASTROINTESTINAL CATEGORY.						
NAVIGATION NOTE: Hemoptysis is graded as Hemorrhage, pulmonary/upper respiratory – <i>Select</i> in the HEMORRHAGE/BLEEDING CATEGORY.						
Hiccoughs (hiccups, singultus)	Hiccoughs	Symptomatic, intervention not indicated	Symptomatic, intervention indicated	Symptomatic, significantly interfering with sleep or ADL	—	—
Hypoxia	Hypoxia	—	Decreased O ₂ saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased O ₂ saturation at rest; continuous oxygen indicated	Life-threatening; intubation or ventilation indicated	Death

PULMONARY/UPPER RESPIRATORY						
Page 3 of 4						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Nasal cavity/paranasal sinus reactions	Nasal/paranasal reactions	Asymptomatic mucosal crusting, blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow	Stenosis with significant nasal obstruction; interfering with ADL	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10 ⁹ /L) – <i>Select</i> ; Infection with normal ANC or Grade 1 or 2 neutrophils – <i>Select</i> ; Infection with unknown ANC – <i>Select</i> .						
Obstruction/stenosis of airway – <i>Select</i> : – Bronchus – Larynx – Pharynx – Trachea	Airway obstruction – <i>Select</i>	Asymptomatic obstruction or stenosis on exam, endoscopy, or radiograph	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; tracheotomy or intubation indicated	Death
Pleural effusion (non-malignant)	Pleural effusion	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g., causing hemodynamic instability or ventilatory support indicated)	Death
ALSO CONSIDER: Atelectasis; Cough; Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
NAVIGATION NOTE: Pleuritic pain is graded as Pain – <i>Select</i> in the PAIN CATEGORY.						
Pneumonitis/pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O ₂ indicated	Life-threatening; ventilatory support indicated	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10 ⁹ /L) – <i>Select</i> ; Infection with normal ANC or Grade 1 or 2 neutrophils – <i>Select</i> ; Infection with unknown ANC – <i>Select</i> ; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Pneumothorax	Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic; intervention indicated (e.g., hospitalization for observation, tube placement without sclerosis)	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated	Death
Prolonged chest tube drainage or air leak after pulmonary resection	Chest tube drainage or leak	—	Sclerosis or additional tube thoracostomy indicated	Operative intervention indicated (e.g., thoracotomy with stapling or sealant application)	Life-threatening; debilitating; organ resection indicated	Death

PULMONARY/UPPER RESPIRATORY							Page 4 of 4
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
Prolonged intubation after pulmonary resection (>24 hrs after surgery)	Prolonged intubation	—	Extubated within 24 – 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Tracheostomy indicated	Death	
NAVIGATION NOTE: Pulmonary embolism is graded as Grade 4 either as Thrombosis/embolism (vascular access-related) or Thrombosis/thrombus/embolism in the VASCULAR CATEGORY.							
Pulmonary fibrosis (radiographic changes)	Pulmonary fibrosis	Minimal radiographic findings (or patchy or bi-basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 – <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50 – <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death	
REMARK: Fibrosis is usually a “late effect” seen >3 months after radiation or combined modality therapy (including surgery). It is thought to represent scar/fibrotic lung tissue. It may be difficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy.							
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10 ⁹ /L) – <i>Select</i> ; Infection with normal ANC or Grade 1 or 2 neutrophils – <i>Select</i> ; Infection with unknown ANC – <i>Select</i> .							
NAVIGATION NOTE: Recurrent laryngeal nerve dysfunction is graded as Laryngeal nerve dysfunction in the NEUROLOGY CATEGORY.							
Vital capacity	Vital capacity	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death	
Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	Voice changes	Mild or intermittent hoarseness or voice change, but fully understandable	Moderate or persistent voice changes, may require occasional repetition but understandable on telephone	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g., electrolarynx) for ≤50% of communication	Disabling; non-understandable voice or aphonic; requires voice aid (e.g., electrolarynx) for >50% of communication or requires >50% written communication	Death	
ALSO CONSIDER: Laryngeal nerve dysfunction; Speech impairment (e.g., dysphasia or aphasia).							
Pulmonary/Upper Respiratory – Other (Specify, __)	Pulmonary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death	

RENAL/GENITOURINARY							Page 1 of 3
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
Bladder spasms	Bladder spasms	Symptomatic, intervention not indicated	Symptomatic, antispasmodics indicated	Narcotics indicated	Major surgical intervention indicated (e.g., cystectomy)	—	
Cystitis	Cystitis	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated	Death	
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10 ⁹ /L) – <i>Select</i> ; Infection with normal ANC or Grade 1 or 2 neutrophils – <i>Select</i> ; Infection with unknown ANC – <i>Select</i> ; Pain – <i>Select</i> .							
Fistula, GU – <i>Select</i> : – Bladder – Genital tract-female – Kidney – Ureter – Urethra – Uterus – Vagina	Fistula, GU – <i>Select</i>	Asymptomatic, radiographic findings only	Symptomatic; noninvasive intervention indicated	Symptomatic interfering with ADL; invasive intervention indicated	Life-threatening consequences; operative intervention requiring partial or full organ resection; permanent urinary diversion	Death	
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated.							
Incontinence, urinary	Incontinence, urinary	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous, pads indicated	Interfering with ADL; intervention indicated (e.g., clamp, collagen injections)	Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)	—	
Leak (including anastomotic), GU – <i>Select</i> : – Bladder – Fallopian tube – Kidney – Spermatic cord – Stoma – Ureter – Urethra – Uterus – Vagina – Vas deferens	Leak, GU – <i>Select</i>	Asymptomatic, radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic, interfering with GU function; invasive or endoscopic intervention indicated	Life-threatening	Death	
REMARK: Leak (including anastomotic), GU – <i>Select</i> refers to clinical signs and symptoms or radiographic confirmation of anastomotic leak but without development of fistula.							

RENAL/GENITOURINARY							Page 2 of 3
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
Obstruction, GU – <i>Select</i> : – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Obstruction, GU – <i>Select</i>	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring complete organ resection indicated	Death	
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – <i>Select Organ or Structure</i> in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.							
Perforation, GU – <i>Select</i> : – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Perforation, GU – <i>Select</i>	Asymptomatic radiographic findings only	Symptomatic, associated with altered renal/GU function	Symptomatic, operative intervention indicated	Life-threatening consequences or organ failure; operative intervention requiring organ resection indicated	Death	
Prolapse of stoma, GU	Prolapse stoma, GU	Asymptomatic; special intervention, extraordinary care not indicated	Extraordinary local care or maintenance; minor revision under local anesthesia indicated	Dysfunctional stoma; operative intervention or major stoma revision indicated	Life-threatening consequences	Death	
REMARK: Other stoma complications may be graded as Fistula, GU – <i>Select</i> ; Leak (including anastomotic), GU – <i>Select</i> ; Obstruction, GU – <i>Select</i> ; Perforation, GU – <i>Select</i> ; Stricture/stenosis (including anastomotic), GU – <i>Select</i> .							
Renal failure	Renal failure	—	—	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death	
ALSO CONSIDER: Glomerular filtration rate.							

RENAL/GENITOURINARY							Page 3 of 3
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
Stricture/stenosis (including anastomotic), GU – <i>Select</i> : – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Stricture, anastomotic, GU – <i>Select</i>	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring organ resection indicated	Death	
ALSO CONSIDER: Obstruction, GU – <i>Select</i> .							
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	Urinary electrolyte wasting	Asymptomatic, intervention not indicated	Mild, reversible and manageable with replacement	Irreversible, requiring continued replacement	—	—	
ALSO CONSIDER: Acidosis (metabolic or respiratory); Bicarbonate, serum-low; Calcium, serum-low (hypocalcemia); Phosphate, serum-low (hypophosphatemia).							
Urinary frequency/urgency	Urinary frequency	Increase in frequency or nocturia up to 2 x normal; enuresis	Increase >2 x normal but <hourly	≥1 x/hr; urgency; catheter indicated	—	—	
Urinary retention (including neurogenic bladder)	Urinary retention	Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period	Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	More than daily catheterization indicated; urological intervention indicated (e.g., TURP, suprapubic tube, urethrotomy)	Life-threatening consequences; organ failure (e.g., bladder rupture); operative intervention requiring organ resection indicated	Death	
REMARK: The etiology of retention (if known) is graded as Obstruction, GU – <i>Select</i> ; Stricture/stenosis (including anastomotic), GU – <i>Select</i> . ALSO CONSIDER: Obstruction, GU – <i>Select</i> ; Stricture/stenosis (including anastomotic), GU – <i>Select</i> .							
Urine color change	Urine color change	Present	—	—	—	—	
REMARK: Urine color refers to change that is not related to other dietary or physiologic cause (e.g., bilirubin, concentrated urine, and hematuria).							
Renal/Genitourinary – Other (Specify, __)	Renal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death	

SECONDARY MALIGNANCY						Page 1 of 1
Adverse Event	Short Name	Grade				
		1	2	3	4	5
Secondary Malignancy – possibly related to cancer treatment (Specify: __)	Secondary Malignancy (possibly related to cancer treatment)	—	—	Non-life-threatening basal or squamous cell carcinoma of the skin	Solid tumor, leukemia or lymphoma	Death
REMARK: Secondary malignancy excludes metastasis from initial primary. Any malignancy possibly related to cancer treatment (including AML/MDS) should be reported via the routine reporting mechanisms outlined in each protocol. Important: Secondary Malignancy is an exception to NCI Expedited Adverse Event Reporting Guidelines. Secondary Malignancy is "Grade 4, present" but NCI does not require AdEERS Expedited Reporting for any (related or unrelated to treatment) Secondary Malignancy. A diagnosis of AML/MDS following treatment with an NCI-sponsored investigational agent is to be reported using the form available from the CTEP Web site at http://ctep.cancer.gov . Cancers not suspected of being treatment-related are <u>not</u> to be reported here.						

SEXUAL/REPRODUCTIVE FUNCTION						Page 1 of 2
Adverse Event	Short Name	Grade				
		1	2	3	4	5
Breast function/lactation	Breast function	Mammary abnormality, not functionally significant	Mammary abnormality, functionally significant	—	—	—
Breast nipple/areolar deformity	Nipple/areolar	Limited areolar asymmetry with no change in nipple/areolar projection	Asymmetry of nipple areolar complex with slight deviation in nipple projection	Marked deviation of nipple projection	—	—
Breast volume/hypoplasia	Breast	Minimal asymmetry; minimal hypoplasia	Asymmetry exists, ≤1/3 of the breast volume; moderate hypoplasia	Asymmetry exists, >1/3 of the breast volume; severe hypoplasia	—	—
REMARK: Breast volume is referenced with both arms straight overhead.						
NAVIGATION NOTE: Dysmenorrhea is graded as Pain – <i>Select</i> in the PAIN CATEGORY.						
NAVIGATION NOTE: Dyspareunia is graded as Pain – <i>Select</i> in the PAIN CATEGORY.						
NAVIGATION NOTE: Dysuria (painful urination) is graded as Pain – <i>Select</i> in the PAIN CATEGORY.						
Erectile dysfunction	Erectile dysfunction	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not indicated	Decrease in erectile function (frequency/rigidity of erections), erectile aids indicated	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	—	—
Ejaculatory dysfunction	Ejaculatory dysfunction	Diminished ejaculation	Anejaculation or retrograde ejaculation	—	—	—
NAVIGATION NOTE: Feminization of male is graded in the ENDOCRINE CATEGORY.						
Gynecomastia	Gynecomastia	—	Asymptomatic breast enlargement	Symptomatic breast enlargement; intervention indicated	—	—
ALSO CONSIDER: Pain – <i>Select</i> .						
Infertility/sterility	Infertility/sterility	—	Male: oligospermia/low sperm count Female: diminished fertility/ovulation	Male: sterile/azoospermia Female: infertile/anovulatory	—	—
Irregular menses (change from baseline)	Irregular menses	1 – 3 months without menses	>3 – 6 months without menses but continuing menstrual cycles	Persistent amenorrhea for >6 months	—	—

SEXUAL/REPRODUCTIVE FUNCTION							Page 2 of 2
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
Libido	Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	—	—	—	
NAVIGATION NOTE: Masculinization of female is graded in the ENDOCRINE CATEGORY.							
Orgasmic dysfunction	Orgasmic function	Transient decrease	Decrease in orgasmic response requiring intervention	Complete inability of orgasmic response; not responding to intervention	—	—	
NAVIGATION NOTE: Pelvic pain is graded as Pain – <i>Select</i> in the PAIN CATEGORY.							
NAVIGATION NOTE: Ulcers of the labia or perineum are graded as Ulceration in DERMATOLOGY/SKIN CATEGORY.							
Vaginal discharge (non-infectious)	Vaginal discharge	Mild	Moderate to heavy; pad use indicated	—	—	—	
Vaginal dryness	Vaginal dryness	Mild	Interfering with sexual function; dyspareunia; intervention indicated	—	—	—	
ALSO CONSIDER: Pain – <i>Select</i> .							
Vaginal mucositis	Vaginal mucositis	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	—	
Vaginal stenosis/length	Vaginal stenosis	Vaginal narrowing and/or shortening not interfering with function	Vaginal narrowing and/or shortening interfering with function	Complete obliteration; not surgically correctable	—	—	
Vaginitis (not due to infection)	Vaginitis	Mild, intervention not indicated	Moderate, intervention indicated	Severe, not relieved with treatment; ulceration, but operative intervention not indicated	Ulceration and operative intervention indicated	—	
Sexual/Reproductive Function – Other (Specify, __)	Sexual – Other (Specify)	Mild	Moderate	Severe	Disabling	Death	

SURGERY/INTRA-OPERATIVE INJURY							Page 1 of 2
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
NAVIGATION NOTE: Intra-operative hemorrhage is graded as Hemorrhage/bleeding associated with surgery, intra-operative or postoperative in the HEMORRHAGE/BLEEDING CATEGORY.							
Intra-operative injury – <i>Select Organ or Structure</i>	Intraop injury – <i>Select</i>	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—	
<i>'Select'</i> AEs appear at the end of the CATEGORY. REMARK: The <i>'Select'</i> AEs are defined as significant, unanticipated injuries that are recognized at the time of surgery. These AEs do not refer to additional surgical procedures that must be performed because of a change in the operative plan based on intra-operative findings. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.							
Intra-operative Injury – Other (Specify, __)	Intraop Injury – Other (Specify)	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—	
REMARK: Intra-operative Injury – Other (Specify, __) is to be used only to report an organ/structure not included in the <i>'Select'</i> AEs found at the end of the CATEGORY. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.							

SURGERY/INTRA-OPERATIVE INJURY – SELECT					Page 2 of 2
AUDITORY/EAR	ENDOCRINE (continued)	GASTROINTESTINAL (continued)	NEUROLOGY (continued)	PULMONARY/UPPER	
– Inner ear	– Thyroid	– Stoma (GI)	NERVES:	RESPIRATORY	
– Middle ear	HEAD AND NECK	– Stomach	– CN V (trigeminal) motor	– Bronchus	
– Outer ear NOS	– Gingiva	HEPATOBIILIARY/ PANCREAS	– CN V (trigeminal) sensory	– Lung	
– Outer ear-Pinna	– Larynx	– Biliary tree-common bile duct	– CN VI (abducens)	– Mediastinum	
CARDIOVASCULAR	– Lip/perioral area	– Biliary tree-common hepatic duct	– CN VII (facial) motor-face	– Pleura	
– Artery-aorta	– Face NOS	– Biliary tree-left hepatic duct	– CN VII (facial) sensory-taste	– Thoracic duct	
– Artery-carotid	– Nasal cavity	– Biliary tree-right hepatic duct	– CN VIII (vestibulocochlear)	– Trachea	
– Artery-cerebral	– Nasopharynx	– Biliary tree NOS	– CN IX (glossopharyngeal) motor pharynx	– Upper airway NOS	
– Artery-extremity (lower)	– Neck NOS	– Gallbladder	– CN IX (glossopharyngeal) sensory ear-pharynx-tongue	RENAL/GENITOURINARY	
– Artery-extremity (upper)	– Nose	– Liver	– CN X (vagus)	– Bladder	
– Artery-hepatic	– Oral cavity NOS	– Pancreas	– CN XI (spinal accessory)	– Cervix	
– Artery-major visceral artery	– Parotid gland	– Pancreatic duct	– CN XII (hypoglossal)	– Fallopian tube	
– Artery-pulmonary	– Pharynx	MUSCULOSKELETAL	– Cranial nerve or branch NOS	– Kidney	
– Artery NOS	– Salivary duct	– Bone	– Lung thoracic	– Ovary	
– Heart	– Salivary gland	– Cartilage	– Peripheral motor NOS	– Pelvis NOS	
– Spleen	– Sinus	– Extremity-lower	– Peripheral sensory NOS	– Penis	
– Vein-extremity (lower)	– Teeth	– Extremity-upper	– Recurrent laryngeal	– Prostate	
– Vein-extremity (upper)	– Tongue	– Joint	– Sacral plexus	– Scrotum	
– Vein-hepatic	– Upper aerodigestive NOS	– Ligament	– Sciatic	– Testis	
– Vein-inferior vena cava	GASTROINTESTINAL	– Muscle	– Thoracodorsal	– Ureter	
– Vein-jugular	– Abdomen NOS	– Soft tissue NOS	OCULAR	– Urethra	
– Vein-major visceral vein	– Anal sphincter	– Tendon	– Conjunctiva	– Urinary conduit	
– Vein-portal vein	– Anus	NEUROLOGY	– Cornea	– Urinary tract NOS	
– Vein-pulmonary	– Appendix	– Brain	– Eye NOS	– Uterus	
– Vein-superior vena cava	– Cecum	– Meninges	– Lens	– Vagina	
– Vein NOS	– Duodenum	– Spinal cord	– Retina	– Vulva	
DERMATOLOGY/SKIN	– Esophagus	NERVES:			
– Breast	– Ileum	– Brachial plexus			
– Nails	– Jejunum	– CN I (olfactory)			
– Skin	– Oral	– CN II (optic)			
ENDOCRINE	– Peritoneal cavity	– CN III (oculomotor)			
– Adrenal gland	– Rectum	– CN IV (trochlear)			
– Parathyroid	– Small bowel NOS				
– Pituitary					

SYNDROMES							Page 1 of 2
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
NAVIGATION NOTE: Acute vascular leak syndrome is graded in the VASCULAR CATEGORY.							
NAVIGATION NOTE: Adrenal insufficiency is graded in the ENDOCRINE CATEGORY.							
NAVIGATION NOTE: Adult Respiratory Distress Syndrome (ARDS) is graded in the PULMONARY/UPPER RESPIRATORY CATEGORY.							
Alcohol intolerance syndrome (antabuse-like syndrome)	Alcohol intolerance syndrome	—	—	Present	—	Death	
REMARK: An antabuse-like syndrome occurs with some new anti-androgens (e.g., nilutamide) when patient also consumes alcohol.							
NAVIGATION NOTE: Autoimmune reaction is graded as Autoimmune reaction/hypersensitivity (including drug fever) in the ALLERGY/IMMUNOLOGY CATEGORY.							
Cytokine release syndrome/acute infusion reaction	Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death	
REMARK: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever), Arthralgia (joint pain), Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea, Pruritis/itching, Rash/desquamation, Rigors/chills, Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.							
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Bronchospasm, wheezing; Dyspnea (shortness of breath); Hypertension; Hypotension; Hypoxia; Prolonged QTc interval; Supraventricular and nodal arrhythmia – <i>Select</i> ; Ventricular arrhythmia – <i>Select</i> .							
NAVIGATION NOTE: Disseminated intravascular coagulation (DIC) is graded in the COAGULATION CATEGORY.							
NAVIGATION NOTE: Fanconi's syndrome is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.							
Flu-like syndrome	Flu-like syndrome	Symptoms present but not interfering with function	Moderate or causing difficulty performing some ADL	Severe symptoms interfering with ADL	Disabling	Death	
REMARK: Flu-like syndrome represents a constellation of symptoms which may include cough with catarrhal symptoms, fever, headache, malaise, myalgia, prostration, and is to be used when the symptoms occur in a cluster consistent with one single pathophysiological process.							
NAVIGATION NOTE: Renal tubular acidosis is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.							

SYNDROMES						
Page 2 of 2						
Adverse Event	Short Name	Grade				
		1	2	3	4	5
"Retinoic acid syndrome"	"Retinoic acid syndrome"	Fluid retention; less than 3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Mild to moderate signs/symptoms; steroids indicated	Severe signs/symptoms; hospitalization indicated	Life-threatening; ventilatory support indicated	Death
REMARK: Patients with acute promyelocytic leukemia may experience a syndrome similar to "retinoic acid syndrome" in association with other agents such as arsenic trioxide. The syndrome is usually manifested by otherwise unexplained fever, weight gain, respiratory distress, pulmonary infiltrates and/or pleural effusion, with or without leukocytosis.						
ALSO CONSIDER: Acute vascular leak syndrome; Pleural effusion (non-malignant); Pneumonitis/pulmonary infiltrates.						
NAVIGATION NOTE: SIADH is graded as Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH) in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Stevens-Johnson syndrome is graded as Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) in the DERMATOLOGY/SKIN CATEGORY.						
NAVIGATION NOTE: Thrombotic microangiopathy is graded as Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) in the COAGULATION CATEGORY.						
Tumor flare	Tumor flare	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics interfering with function and interfering with ADL	Disabling	Death
REMARK: Tumor flare is characterized by a constellation of signs and symptoms in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances.						
ALSO CONSIDER: Calcium, serum-high (hypercalcemia).						
Tumor lysis syndrome	Tumor lysis syndrome	—	—	Present	—	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia).						
Syndromes – Other (Specify, ___)	Syndromes – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

VASCULAR						
Page 1 of 2						
Adverse Event	Short Name	Grade				
		1	2	3	4	5
Acute vascular leak syndrome	Acute vascular leak syndrome	—	Symptomatic, fluid support not indicated	Respiratory compromise or fluids indicated	Life-threatening; pressor support or ventilatory support indicated	Death
Peripheral arterial ischemia	Peripheral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed non-surgically and without permanent deficit	Recurring or prolonged (≥24 hrs) and/or invasive intervention indicated	Life-threatening, disabling and/or associated with end organ damage (e.g., limb loss)	Death
Phlebitis (including superficial thrombosis)	Phlebitis	—	Present	—	—	—
ALSO CONSIDER: Injection site reaction/extravasation changes.						
Portal vein flow	Portal flow	—	Decreased portal vein flow	Reversal/retrograde portal vein flow	—	—
Thrombosis/embolism (vascular access-related)	Thrombosis/embolism (vascular access)	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Thrombosis/thrombus/embolism	Thrombosis/thrombus/embolism	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Vessel injury-artery – Select: – Aorta – Carotid – Extremity-lower – Extremity-upper – Other NOS – Visceral	Artery injury – Select	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage (e.g., stroke, MI, organ or limb loss)	Death
NAVIGATION NOTE: Vessel injury to an artery intra-operatively is graded as Intra-operative injury – Select Organ or Structure in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						



VASCULAR							Page 2 of 2
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
Vessel injury-vein – Select: – Extremity-lower – Extremity-upper – IVC – Jugular – Other NOS – SVC – Viscera	Vein injury – <i>Select</i>	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage	Death	
NAVIGATION NOTE: Vessel injury to a vein intra-operatively is graded as Intra-operative injury – <i>Select Organ or Structure</i> in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.							
Visceral arterial ischemia (non-myocardial)	Visceral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (≥24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening; disabling; evidence of end organ damage	Death	
ALSO CONSIDER: CNS cerebrovascular ischemia.							
Vascular – Other (Specify, ___)	Vascular – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death	