Tjock- och ändtarmscancer

Utdrag ur nationellt vårdprogram: Kapitel 7, Ärftlig kolorektal cancer (och referenser)

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REGIONALA CANCERCENTRUM I SAMVERKAN

KAPITEL 7

Ärftlig kolorektal cancer

Rekommendationer

- Ärftlighet för cancer bör alltid efterfrågas vid kolorektalcancer-diagnos
- Testning för defekt mismatch repair (dMMR) med MSI eller IHC i tumörvävnad bör göras vid diagnos av kolorektal cancer (se 10.9)

Individer med påvisat förhöjd risk:

- Lynchs syndrom: koloskopi-kontroller från 20–25 års ålder med 2 års intervall (+++)
- Samtliga polyposyndrom:
  - årlig koloskopi från ca 12–15 års ålder
  - profylaktisk kolektomi rekommenderas alla bärare när polypantalet blir svåröverskådligt (++++ för FAP)

Individer med ärftligt ökad risk utan påvisad patogen variant rekommenderas koloskopikontroller (+++) enligt:

- 1 förstagradssläkting med kolorektalcancer <50 år: engångskoloskopi vid 55 års ålder
- 1 förstagradssläkting med kolorektalcancer ≥ 50 år: ingen koloskopi
- Barn/syskon/förälder till kluster av 2 förstagradssläktingar med kolorektalcancer: engångskoloskopi vid 55 års ålder
- Barn/syskon/förälder till kluster av 3 förstagradssläktingar med kolorektalcancer: koloskopi vart 5:e år med start 5 år innan yngsta fall

7.1 Ärftliga tillstånd

7.1.1 Bakgrund

Ärftliga faktorer beräknas ligga bakom 20–25 % av all kolorektal cancer. I 2–4 % kan hela riskökningen knytas till en bakomliggande monogen orsak, d.v.s. en patogen variant (mutation) i ett enskilt arvsanlag/gen. Vid handläggning av patienter med kolorektal cancer är det viktigt att fråga om det finns andra cancerinsjuknanden i släkten.

En enkel ärftlighetsanamnes inkluderar:

- typ av cancer
- insjuknandeålder
- hur de som insjuknat är släkt

Nedan beskrivs kortfattat de ärftliga tillstånden Lynchs syndrom (tidigare kallat HNPCC – hereditär nonpolyposis kolorektal cancer), familjär adenomatös polypos (FAP) och MUTYH–

associerad polypos. Familjär kolorektal cancer är en benämning för de fall där en ärftligt ökad risk finns utan att en bakomliggande patogen variant kan påvisas.

Syftet med att identifiera ett ärftlig insjuknande i kolorektal cancer är att denna information kan ge information om prognos och vara behandlingsstyrande. Det ger också information om hur patient skall följas upp utifrån den upprepade risken för nytt primärt insjuknande i kolorektal cancer samt tydligt ökad risk för cancersjukdom i andra organ, till exempel livmoderkroppscancer hos kvinnor vid Lynchs syndrom. När en ärftlig patogen variant (mutation) har identifierats så finns möjligheten för patient att dela denna information med sina släktingar som i sin tur kan erhålla genetisk vägledning och genomgå genetisk analys om man så önskar. Är man bärare av mutationen så är det viktigt att kunna erbjudas kontrollprogram för att förhindra insjuknande i cancer. Uppföljning av personer med påvisad ärftlighet för Lynchs syndrom bör följas av specialist med god kännedom om den kliniska bilden vid detta syndrom och att förutsättningarna finns för ett multiprofessionellt omhändertagande. Vid de ovanliga ärftliga syndromen med påvisad mutation med polypbildning och/eller koloncancer är detta än mer viktig. Det är också angeläget att det finns en kontaktperson/enhet som patient är hänvisad till om symtom eller frågor skulle uppstå mellan kontrollerna.

7.1.2 Lynchs syndrom

Lynchs syndrom är ett multitumörsyndrom med särskilt höga risker för bland annat kolorektal cancer [28]. Syndromet orsakas av mutationer i DNA–reparationsgenerna MLH1, MSH2, MSH6 och till del PMS2 som är ansvariga för mismatch repair (MMR). Histopatologiska karaktärsdrag för de kolorektala tumörerna är att de ofta är högersidiga, mucinösa och lågt differentierade samt att det finns tumör-infiltrerande lymfocyter [28-31]. Defekt *mismatch repair* (dMMR) föreligger oftast vid Lynchs syndrom och kan påvisas med MSI-analys (mikrosatellitinstabilitet, MSI-H) eller genom bortfall av MMR-proteiner vid immunhistokemisk analys (IHC) av tumörvävnad [32]. Lynchs syndrom orsakar cirka 1–3 % av all kolorektal cancer. Det ärvs autosomalt dominant, vilket innebär att barn till anlagsbärare löper 50 procents risk att ha ärvt det sjukdomsorsakande anlaget. Förekomsten i befolkningen beräknas vara runt 2–4 promille [33] och syndromet ska misstänkas vid ung insjuknandeålder eller om flera släktingar har insjuknat i Lynch-associerade tumörsjukdomar. I Sverige i dag känner vi till närmare 400 familjer med Lynchs syndrom men det är sannolikt underdiagnostiserat [34].

Livstidsrisken för cancer vid Lynchs syndrom varierar med bakomliggande gen, kön och familjehistoria men uppskattas till 30–70 % för kolorektal cancer och livmoderkroppscancer. Riskerna är också förhöjda för äggstockscancer (5–10 %), cancer i urinvägarna (5–20 %) och cancer i magsäcken (2–18 %) samt i viss mån för tunntarmscancer och hjärntumörer [35, 36].

Som ett stöd för att bedöma den enskilda risken att insjukna i Lynch-associerade tumörer utifrån kön, ålder och mutation finns en beräkningsmodell framtagen.

7.1.3 Familjär kolonpolypos, FAP

FAP kännetecknas av ett stort antal (100–1 000) polyper i framför allt duodenum, kolon och rektum. I 90 % av fallen finns en mutation i APC-genen och nedärvningsmönstret är autosomalt dominant (barn till anlagsbärare löper 50 procents risk att ha ärvt anlaget). Prevalensen är ca 35 per miljon och i Sverige finns ca 200 familjer med FAP. I ca 20 % av fallen föreligger en nymutation och familjehistoria saknas.

Polyputvecklingen sker successivt och vid 40 års ålder räknar man med att alla anlagsbärare har utvecklat polypos. Om förebyggande operation inte görs utvecklar närmare 100 % av alla bärare kolorektal cancer med en medianålder för insjuknande vid 40 år. Merparten (70–80 %) av tumörerna är belägna i vänsterkolon och rektum. Andra vanliga fynd är polyper i magsäck och duodenum som utvecklas till adenom och cancer i duodenum/periampullärt hos 4–12 % av bärarna.

Övriga tumörtyper som associerats med FAP är desmoider, osteom i käken, papillär sköldkörtelcancer (1–12 %) och hepatoblastom hos barn. Den kliniska bilden är ofta typisk men ibland ses en mildare fenotyp, s.k. attenuerad FAP (AFAP) där polyputvecklingen inte är lika uttalad.

7.1.4 MUTYH-associerad polypos (MAP)

MAP är ett ärftligt polypsyndrom där man kan påvisa patogena varianter i genen MUTYH (tidigare MYH). Syndromet kännetecknas av adenomatösa tjocktarmspolyper, främst i högerkolon. Patogena varianter/mutationer i MUTYH–genen ses hos 17–24 % av individer med klinisk bild som vid FAP/AFAP där ingen APC-mutation påvisats [37] och ger över livet en kraftigt ökad risk för kolorektal cancer men inte för andra cancerformer.

MUTYH nedärvs autosomalt recessivt vilket innebär att risken för ett helsyskon att också drabbas är 25 %. Knappt 1 % av normalpopulationen är heterozygota (friska) bärare av MAP [38, 39].

7.1.5 Övriga syndrom med ökad risk för kolorektal cancer

Utöver ovanstående finns del andra ovanligare syndrom med en ökad risk för kolorektal cancer: Peutz-Jeghers syndrom, Cowdens syndrom (PTEN, hamartomatöst tumörsyndrom) och Juvenil polypos. Dessa syndrom kännetecknas framförallt av polyper i magtarm-kanalen men har även en del andra typiska signum. För utförlig information kring dessa, se riktlinjer via www.insight-group.org.

7.2 Utredning och screening för ärftliga tillstånd

Vid misstanke om ärftligt orsakad kolorektal cancer bör remiss ställas till en onkogenetisk mottagning för bedömning och utredning. Molekylärgenetisk testning görs i första hand med blodprov från en individ som själv insjuknat i cancer. Det är därför av stort värde att säkra blodprov i sent palliativa skeden vid misstanke ärftlighet, exempelvis vid ungt insjuknande. Finns det inte någon levande person i släkten kan motsvarande analys eventuellt göras på DNA från arkiverad vävnad från avliden person med cancerdiagnos.

7.2.1 Remisskriterier för genetisk utredning

- Individ/familj där någon insjuknat i kolorektal cancer eller livmoderkroppscancer före 50 års ålder
- Individ/familj med två eller flera personer med kolorektal cancer i samma släktgren, varav en insjuknat före 60 års ålder
- Individ/familj med två eller flera personer med maligna tumörer associerade till ärftlig kolorektal cancer* i samma släktgren varav en insjuknat före 60 års ålder
- Individ med metakron/synkron tumör associerad till ärftlig kolorektal cancer*

- Misstanke om ärftligt polypossyndrom
- Påvisad dMMR (MSI/IHC) utan BRAF-mutation i tumörvävnad oavsett familjehistoria

* Kolorektal cancer samt cancer i livmoderkropp, äggstockar, tunntarm, magsäck eller urinvägar.

7.2.2 Testning för dMMR vid kolorektalcancer-diagnos

Vid insjuknande i kolorektal cancer bör man göra analys avseende dMMR med antingen MSI eller immunhistokemi (IHC) på tumörvävnad. Mikrosatellitinstabilitet-hög (MSI-H) eller bortfall av MMR-proteiner på IHC kan indirekt tala för bakomliggande mutation i MMR-generna. Mer än 90 % av all kolorektalcancer som orsakas av Lynchs syndrom uppvisar MSI-H men det kan även förekomma vid sporadisk kolorektalcancer [32], framför allt om MLH-1-bortfall påvisas. Sporadiska dMMR-tumörer beror oftast på metylering av MLH1 och uppvisar i regel BRAF-mutation vilket ses i färre än 1% av kolorektal cancer vid Lynchs syndrom [40].

Det finns hälsoekonomiska genomgångar som visar att det är kostnadseffektivt att genomföra testning för Lynchs syndrom med MSI/IHC vid samtliga fall av kolorektalcancer och livmoderkroppscancer och i flera länder rekommenderas detta rutinmässigt [41, 42], bl.a. i Danmark där man över de senaste tio åren har identifierat dubbelt så många anlagsbärare sett till befolkningen jämfört med Sverige. Rekommendationer från National Institute for Health and Care Excellence (NICE) i England 2017 anger dMMR-analys av tumör för samtliga personer med primärinsjuknande i kolorektal cancer. En utvärdering av dessa riktlinjer visar positiva resultat av att identifiera personer med Lynchs syndrom och möjliggör bla en individualiserad behandling av dessa patienter [43, 44].

Skulle dMMR utan BRAF-mutation påvisas i en tumör ska Lynchs syndrom uteslutas, detta gäller även vid primärtumör i övre urinvägar eller livmoderkropp.

Vid misstanke om polypossyndrom bör molekylärgenetisk testning göras för att bekräfta diagnosen.

Vid påvisad sjukdomsorsakande variant i någon av kolorektalcancer-generna finns möjlighet till anlagsbärartest för friska släktingar. Cancergenetisk vägledning och ett uppföljningsprogram skall erbjudas anlagsbärare.

7.3 Uppföljning av symtomfria individer med ärftligt förhöjd risk

7.3.1 Lynchs syndrom

Kontrollprogram för friska anlagsbärare:

Det finns flera rapporter som visar en minskning av risken att insjukna i kolorektal cancer vid Lynchs syndrom på 50–60 % vid regelbunden koloskopi. Rekommendation om optimalt intervall har ändrat sig genom åren men i dag rekommenderas koloskopi-kontroller från 20–25 års ålder med 2 års intervall då man vid längre intervall sett ökad förekomst av intervallcancer [47–49]. Vid patogen variant i PMS2 är riskerna för cancer inte lika höga som för övriga gener och kontroller kan startas vid 35–40 års ålder om inte släktanamnes skulle indikera kontroller innan dess.

ASA kan vara av värde i kemopreventivt syfte och har i studier visat en riskreduktion på 50 % för kolorektal cancer vid Lynchs syndrom [45]. Den optimala dosen och behandlingstiden är inte

fastställd så behandling rekommenderas främst inom ramen för studier, men NICE förväntas under början av 2020 utfärda rekommendation kring behandling vid Lynchs syndrom.

Anlagsbärare bör informeras om alarmsymtom och livsstilsfaktorer knutna till ökad risk för kolorektal cancer. Både rökning och övervikt är kopplade till ökad cancerrisk bland mutationsbärare [46-48].

Utöver kontroller för kolorektalcancer erbjuds kontakt med gynekolog för ställningstagande till profylaktisk salpingoofohysterektomi samt urologiska kontroller vid konstaterad MSH2-variant. Övriga kontroller bedöms utifrån förekomst av annan cancer i släkten.

Koloskopi bör ske upp till 70–75 års ålder och eventuellt längre. Innan fortsatt koloskopi görs en sammantagen klinisk bedömning. Hänsyn tas då till allmänt hälsotillstånd, tidigare fynd vid koloskopier samt patientens egen motivation.

7.3.2 Polypossyndrom

7.3.2.1 FAP

Vid verifierad FAP rekommenderas en första koloskopi vid ca 12–15 års ålder och sedan regelbundet (vanligtvis årligen) fram till dess att adenomantalet börjar bli stort vilken vanligen innebär kolektomi i 20-årsåldern. Det finns ingen farmakologisk behandling som kan ersätta kirurgi vid FAP. NSAID (vanligen COX-II hämmare) har visat sig minska såväl storleken som antalet kolorektala adenom, men det saknas belägg för att cancerrisken minskar [49]. Personer med många rektala polyper eller bristande koloskopiföljsamhet bör rekommenderas proktokolektomi med bäckenreservoar alternativt permanent ileostomi på grund av den kvarstående risken för rektalcancer. Individer med få rektala adenom och god följsamhet kan erbjudas kolektomi med ileorektal anastomos (IRA) eftersom de funktionella resultaten är bättre och risken för en senare rektalcancer är lägre. Kolektomi med IRA blir ofta förstahandsvalet för yngre kvinnor med önskan om framtida graviditet eftersom bäckenreservoarkirurgi inverkar negativt på möjligheten till lyckad befruktning.

Efter kolorektal kirurgi ska individer med bäckenreservoar, kontinent ileumreservoar ad modum Kock eller IRA följas upp regelbundet med skopi vartannat år respektive var 6:e månad p.g.a. cancerrisk i reservoaren eller i rektum.

Vid AFAP är utbredningen av polyper mildare och profylaktisk kirurgi är inte alltid nödvändig om polyputbredningen är överskådlig och patienten har god följsamhet till undersökningar.

Endoskopisk uppföljning av ventrikel/duodenum rekommenderas med start i 20–25-årsåldern, intervallet bestäms utifrån fynd av polyper utifrån Spigelmanklassifikationen. Vid flertalet negativt prognostiska undersökningsfynd (antal, storlek, histologi, grad av dysplasi) kan profylaktisk kirurgi diskuteras

Inga övriga kontroller rekommenderas rutinmässigt.

7.3.2.2 MAP

Vid MUTYH-associerad polypos är polyperna färre till antalet än vid FAP och i större utsträckning belägna i högerkolon. Homozygota anlagsbärare rekommenderas kontroller på samma sätt som vid FAP. I dagsläget rekommenderas inga utökade kontroller för heterozygota anlagsbärare.

7.3.2.3 Övriga polypossyndrom

För Juvenil polypos, Peutz-Jeghers syndrom och Cowdens syndrom hänvisas till särskilda kontrollprogram. Kontakt kan tas med onkogenetiska mottagningar för diskussion.

7.3.3 Familjär kolorektal cancer

Om man på goda grunder har uteslutit bakomliggande patogen variant och det anses finnas en ärftligt ökad risk brukar man definiera det som familjär kolorektal cancer. En genomgång av evidens och rekommendationer gällande kontrollprogram vid familjär kolorektal cancer har nyligen publicerats i brittiska riktlinjer [50]. Kontroller rekommenderas enligt nedan:

- 1 förstagradssläkting med kolorektalcancer <50 år: engångskoloskopi vid 55 års ålder
- 1 förstagradssläkting med kolorektalcancer ≥50 år: ingen koloskopi
- Barn/förälder/syskon till kluster av 2 förstagradssläktingar med kolorektalcancer: engångskoloskopi vid 55 års ålder
- Barn/förälder/syskon till kluster av 3 förstagradssläktingar med kolorektalcancer: koloskopi vart 5:e år med start 5 år innan yngsta fall

Vid normalfynd vid engångskoloskopi rekommenderas fortsatta kontroller inom allmän screening för kolorektal cancer. Vid fynd av polyper/adenom rekommenderas uppföljning enligt polypuppföljningsprogram.

7.4 Särskilda aspekter på behandling av personer med ärftlig kolorektalcancer

7.4.1 Lynch-associerad kolorektal cancer

Lynchs syndrom medför ännu inte några säkra onkologiska behandlingsprediktiva rekommendationer men en del data talar för minskad nytta av adjuvant cytostatika vid stadium II-tumörer samt respons på immunterapi vid metastaserad sjukdom om dMMR föreligger.

För individer med Lynchs syndrom bedöms risken för metakron kolorektal cancer vara betydande. Den kirurgiska behandlingen av koloncancer bör därför följa en av två möjliga strategier:

- Kolektomi med ileorektal anastomos (proktokolektomi med bäckenreservoar alternativt permanent ileostomi om tumören är belägen i rektum). Jämfört med segmentresektion har kolektomi visats minska risken för nya cancerinsjuknanden, särskilt hos unga. Risken för ny kolorektalcancer hos individer som genomgått segmentresektion är 20–60 % [51, 52].
- Resektion enligt vedertagna onkologiska principer vid kolorektal cancer, det vill säga segmentresektion. Denna behandling lämpar sig bäst för äldre individer och förutsätter fortsatta kontroller p.g.a. risken för metakron cancer.

Vid rektalcancer samt misstänkt men inte säkerställt Lynchs syndrom bör alternativ 2 väljas.

Hos kvinnor med Lynchs syndrom som opereras för kolorektal cancer kan/bör samtidig resektion av livmoder/äggstockar övervägas.

Postoperativ uppföljning avseende metastasering hos individer med Lynchs syndrom som opererats för kolorektal cancer ska följa de generella riktlinjerna. Koloskopiuppföljningen hos dessa individer ska dock följa intervallen för Lynchs syndrom.

7.4.2 Familjär kolorektal cancer

Familjär kolorektal cancer handläggs kirurgiskt som sporadisk.

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KAPITEL 24

Vårdprogramgruppen

24.1 Vårdprogramgruppens medlemmar

Ordförande: Bärbel Jung

Norr: Håkan Olsson

Stockholm-Gotland: Annika Sjövall

Syd: Jakob Eberhard, Birger Pålsson

Sydöst: Mats Persborn

Väst: Dan Asplund, Susanne Ottosson

Uppsala-Örebro: Kenneth Smedh

Ansvarig patolog: Rickard Palmqvist

Ansvarig radiolog: Lennart Blomqvist

Ansvarig strålonkolog: Anders Johnsson

Omvårdnadsansvarig: Fotini Koutakis Wolin

Adjungerad onkolog: Bengt Glimelius

24.2 Författare

Bärbel Jung, med dr, överläkare, kirurgkliniken Universitetssjukhuset Linköping

Anders Johnsson, docent, överläkare, onkologkliniken, Skånes universitetssjukhus

Andreas Pischel, med dr, överläkare, specialist i invärtesmedicin och gastroenterologi och hepatologi, Sektion för Gastroenterologi, Sahlgrenska universitetssjukhus

Anna Martling, professor, Karolinska Institutet

Annika Sjövall, docent, överläkare, Kolorektalcancerflödet, Karolinska universitetssjukhuset

Antoni Zawadzki, med. dr, överläkare, kirurgkliniken, Skånes universitetssjukhus

Bengt Glimelius, senior professor, överläkare, Uppsala

Birger Pålsson, docent, överläkare, kirurgkliniken, FoUU, Kronoberg, RCC Syd

Björn Olsson, med dr, överläkare, medicinsk rådgivare, Regionalt Cancercentrum Syd.

Calin Radu, med dr, överläkare, onkologkliniken, Akademiska sjukhuset

Caroline Staff, med. dr, överläkare, St. Görans Sjukhus

Dan Asplund, med dr, överläkare, kirurgkliniken, Sahlgrenska universitetssjukhuset/Östra

Daniel Rydbeck, specialistläkare, kirurgkliniken, Sahlgrenska universitetssjukhuset/Östra

Eva Angenete, professor, överläkare, kirurgkliniken, Sahlgrenska universitetssjukhuset/Östra

Eva Greus, kontaktsjuksköterska, stomiterapeut, Kirurgcentrum Region Västerbotten, Skellefteå

Eva Haglind, fd adjungerad professor, överläkare, kirurgkliniken, Sahlgrenska universitetssjukhuset/Östra

Fredrik Hopfgaren, patientrepresentant, Mag- och tarmförbundet

Fotini Koutakis Wolin, onkologisjuksköterska/kontaktsjuksköterska, onkologkliniken, Centralsjukhuset i Karlstad

Gustav Silander, överläkare, cancergenetiska mottagningen, Regionalt Cancercentrum Norr, Norrlands universitetssjukhus

Henrik Iversen, docent, överläkare, kirurg, Karolinska universitetssjukhuset

Håkan Olsson, överläkare, kirurgcentrum, Norrlands universitetssjukhus

Ingrid Ljuslinder, överläkare, cancercentrum, Norrlands universitetssjukhus

Ingvar Syk, professor, överläkare, kirurgkliniken, Skånes universitetssjukhus

Jakob Eberhard, docent, överläkare, onkologkliniken, Skånes universitetssjukhus

Jenny Drott, med. dr, specialistsjuksköterska, kirurgkliniken, Universitetssjukhuset Linköping

Jennifer Park, med. dr, specialistläkare, kirurgkliniken, Sahlgrenska universitetssjukhuset/Östra

Joakim Folkesson, docent, överläkare, verksamhetsområde kirurgi, Akademiska sjukhuset

Katrine Riklund, professor, radiolog, Norrlands universitetssjukhus

Kenneth Smedh, adj. professor, överläkare, kirurgkliniken, Västmanlands sjukhus, Västerås

Lars Agreus, professor emeritus, Karolinska Institutet, distriktsläkare, Öregrunds VC, Praktikertjänst AB

Lena Söderqvist, sjuksköterska, samordnande kontaktsköterska inom tjock- och ändtarmscancer, Regionalt Cancercentrum Stockholm Gotland

Lennart Blomqvist, professor, radiolog, Karolinska universitetssjukhuset

Lina Hellman, överläkare, kirurgkliniken, Länssjukhuset Ryhov

Louis Banka Johnson docent, överläkare, kirurgkliniken, Skånes universitetssjukhus

Maria Albertsson, professor, överläkare, Linköping

Maria Gustafsson-Liljefors, docent, överläkare, Karolinska universitetssjukhuset

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Peter Nygren, professor, onkologkliniken, Akademiska sjukhuset

Richard Palmqvist, patolog, Norrlands universitetssjukhus

Stefan Skullman, docent, överläkare, kirurgkliniken, Skaraborgs sjukhus

Torbjörn Swartling, med dr, överläkare, kirurgkliniken, Sahlgrenska universitetssjukhuset/Östra

24.3 Jäv och andra bindningar

Vårdprogramarbetet har utförts utan stöd från läkemedelsindustrin eller andra externa parter. Vårdprogramgruppens medlemmar har lämnat in jävsdeklarationer som godkänts av Regionalt cancercentrum och kopior på dessa kan fås från Regionalt cancercentrum norr.