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DIAGNOSIS AND TREATMENT OF ANAL CARCINOMA

An overview

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Squamous cell carcinoma of the anal canal gives early symptoms and is easy to diagnose. However, these patients often present with advanced tumours, probably because of patient's and/or doctor's delay. The diagnosis must be confirmed by a conclusive biopsy as the treatment of ano-rectal tumours is based upon correct histopathological diagnosis. Loco-regional tumour control of squamous cell carcinoma is excellent following radiotherapy or combined chemoradiotherapy as only 10–20% of the patients develop a local recurrence. The great majority of these are cured by abdominoperineal resection. However, this treatment involves considerable acute and chronic toxicity, but mortality is less than 2%. There is no general agreement about how to minimize toxicity without hazarding loco-regional tumour control. One way could be to irradiate only the primary tumour site in patients with early lesions, and reserve radiotherapy of regional lymph nodes for more advanced cases. About 20% of the patients develop distant metastases, which make the disease incurable. Hence, frequent, rectal digital examination is the most important follow-up since early local recurrences can easily be cured. There is no general consensus concerning adjuvant chemotherapy, but its potential should be further explored.

Treatment of squamous cell carcinoma of the anal canal has changed dramatically during the latest 20 years. Surgery (abdominoperineal resection-APR) is now in most centers used only as salvage treatment when conservative treatment (radiotherapy or combined chemoradiotherapy) fails. However, no generally accepted standard (chemo) radiotherapy has been established, and various regimens are being used. The reason for this is probably the fact that the disease is comparatively uncommon and thus most hospitals have only small series of patients. It is a peculiar neoplasm since women are affected 2–5 times more often than men (1–4). The reason for this is unknown (1, 5–7), but papillomavirus may be of importance (6). Even if the anal canal and rectum anatomically is located very close to each other, carcinomas arising in the 2 compartments have somewhat different tumour biology. Squamous cell carcinomas of the anal canal usually infiltrate diffusely into the surrounding tissue beyond the palpable mass and regional lymphatic spread is often present (3, 8, 9). Patients with squamous cell carcinomas should therefore receive radiotherapy or combined chemo/radiotherapy as first-line treatment, while surgery as a rule still is considered to be the main treatment of choice for adenocarcinomas.

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Anatomy and pathology

The anal canal is derived from the embryonic ectoderm while rectum is derived from endoderm. This is the resason why the anal canal is lined by squamous cells and the rectum by glandular mucosa cells. The transient zone between anus and rectum is lined by transitional epithelium. This includes a variety of cells, of which some resemble urinary tract epithelium and others look like stratified columnar epithelium (10, 11). The anal epithelium differs from true skin as it contains no hair, sebaceous or sweat glands. It is limited at its lower end by the anal verge with true skin and at its upper end by glandular mucosa of the rectal ampulla.

Malignant tumours in the anal canal are usually squamous cell carcinomas. However, tumours arising in the transitional zone show a variable histopathological picture with designations such as cloacogenic carcinomas, basaloid carcinomas, etc. (12–16). These terms have so far not been shown to be of any clinical importance. From a clinical point of view, these terms should be included in the group squamous cell carcinomas (17). Carcinomas in the ano-rectal region should therefore be classified either as squamous cell carcinomas or as adenocarcinomas. Other malignant neoplasms like mucoepidermoid carcinoma and melanoma are extremely rare in the anus (1, 11).

The submucosal layer is very narrow in the anal canal, and hence the mucosa is located very close to the anal sphincter. This explains why anal canal carcinomas often infiltrate the sphincter. Lymphatic spread of tumour cells follows the lymph vessels from anus; inguinal lymph nodes (lower part of the anal canal), pelvic lymph nodes (pararectal or iliacal) and the abdominal lymph nodes. A high proportion (10–50%) of the patients have regional lymph node involvement at the time of diagnosis (1–3, 12, 15, 18–31). Hematogeneous spread of tumour cells cause distant metastases preferable in the liver, lung and skin. Distant metastases are observed in 5–10% of the cases at the time of diagnosis, while another 10–15% of the patients develop metastases during follow-up after primary treatment (3, 24). Carcinomas of the anal canal are staged according to the UICC system (32) as shown in the Table.

Table

Staging of carcinomas of the anal canal (UICC 1989)

Primary tumour	
T0	No primary tumour
Tis	Carcinoma in situ
T1	<2 cm in greatest dimension
T2	2–5 cm in greatest dimension
T3	>5 cm in greatest dimension
T4	Invasion of adjacent organ
Regional lymph nodes	
N0	no lymph node metastases
N1	Perirectal lymph nodes involved
N2	Unilateral internal iliac and/or inguinal lymph nodes involved
N3	Bilateral internal iliac and/or inguinal lymph nodes involved or perirectal and inguinal lymph nodes involved.
Distant metastases	
M0	Absent
M1	Present

Diagnosis

The diagnosis is based upon rectal digital examination and biopsy. Carcinomas in the anal canal usually gives symptoms at an early stage (2, 33–37). Moreover, the tumour can easily be reached by a doctor's finger. One would therefore expect that anal carcinomas are diagnosed at an early stage. However, these patients often present with advanced tumours (2, 8, 38–46). The majority of these patients have previously experienced benign anal diseases like hemorrhoids, fissures and abscess (2, 35). They interpret increasing anal symptoms as relapse of these diseases and do not seek medical aid. The most common initial symptoms are anal bleeding, pain and palpable lump (2, 8, 36, 37, 47). Moreover, doctor's delay is present in approximately 20% of the cases (2). This reflects that some doctors do not perform a digital, rectal examination when patients present with anal symptoms, while others do not recognize their finding as a malignant tumour. This is of considerable importance as rectal, digital examination may as well reveal cancer of the lower rectum, a neoplasma far more common than anal cancer (1). The diagnosis may also be delayed in hospitals because some tumours appear to be benign by clinical examination, and therefore no biopsy is taken or histopathological examination of the surgical specimen is not performed (2). This emphasizes the good habit of biopsies and histopathological examination even when malignancy is not clinically suspected. Approximately half of the patients have more than one month's delay from the initial symptom to diagnosis, and about 1/4 have more than 6 months' delay (2). The delay in diagnosis may partly explain why more than 50% of the patients present with advanced tumours (T3–T4) at the time of diagnosis (2, 8, 43–45).

It is important that histopathological examination of the tumour is performed before treatment is initiated to ensure that the present tumour is a squamous cell carcinoma and not an adenocarcinoma. Digital, rectal examination and transanal ultrasonography should be performed to stage the tumour (48, 49). Enlarged lymph nodes should be punctured for cytologic diagnosis, if possible. Ultrasonography of liver and x-ray of lung should be performed to reveal distant metastases (3).

Treatment

Surgery

The standard treatment for anal canal cancer has been abdominoperineal resection (APR) (12, 15, 19, 20, 22, 24, 25, 27, 28, 31, 37, 45, 47, 50–63). A simple local excision has been performed for small tumours (22, 24, 31, 34, 50, 64, 65). However, a high percentage of these patients have experienced local relapse, probably because the tumour often infiltrates beyond the palpable mass or subclinical tumour satellites are left after APR. Local recurrences following primary surgery can seldom be cured by another surgical operation, and these patients usually suffer badly from their increasing pelvic tumour. Extended surgery has been performed (except T0–T1 cases) in order to remove

subclinical tumour tissue (66), but even if the posterior part of vagina and all palpable lymph nodes in the pelvic and the groin have been removed, the frequency of local relapses has not decreased. On the contrary, treatment-related mortality rate has raised towards 10% and the patients have experienced severe late morbidity (12, 19, 24, 25, 27, 31, 56, 66). The high frequency of local relapses has been the main reason why many studies have reported only about 30% survival rate. The results have largely depended on tumour stage at the time of surgery as 90% of the patients with T1-tumours but extremely few patients with T4-tumours have been reported as cured (31, 37, 57).

Radiotherapy

Centres in France and USA started pre-operative radiotherapy in the late 1960s to improve local tumour control (40, 67). The tumour appeared to be quite radiosensitive as no malignant tissue could be observed in many of the surgical specimens from APR. This observation encouraged the use of radiotherapy alone as first-line treatment. During the following years radiotherapy was generally accepted as primary treatment, while surgery was used only in more radioresistant or recurrent cases and for small tumours (Tis and early T1). However, radiotherapy has been used occasionally in the treatment of anal canal carcinoma already since 1920, but the results were generally poor (38, 68–71). Interstital radium or ortovoltage roentgen therapy was used at that time since megavoltage equipment for external beam therapy was not generally available until about 1950. Mostly, advanced tumours were treated but 50% survival was reported for patients with small tumours (69, 71). Despite of these promising reports surgery was the only accepted treatment until recently. Radiotherapy with megavoltage equipment has greatly improved loco-regional control and local relapse is no longer a main problem even in T4 cases (3, 43, 49, 59, 72–76). Moreover, quality of life is improved as anal function usually is preserved. Most reports strongly indicate that radiotherapy is superior to APR regarding both survival, local tumour control and quality of life (73, 76, 77). However, these studies are based upon historical controls as no randomized study between surgery and (chemo)radiotherapy has been published.

Several different radiotherapy techniques have been used concerning field size and fractionation, and some centres also have added cytotoxic agents to increase the effect. No randomized trials between various regimens of (chemo)-radiotherapy have been published (73, 76). Only few reports on treatment results in large materials have been published (2, 3, 8, 46, 71, 78). Two different major treatment regimens are being used: the Nigro (67) and the Papillon (40) regimen. There exists, however, numerous modified regimens based upon either of these two therapeutic philosophies. The former is a loco-regional treatment (3, 35, 44–46, 49, 57, 59, 66, 67, 73–75, 77, 79–89), while the latter (9, 39–42, 71, 73, 74, 76, 78, 90) does not include the pelvic lymph nodes. The Nigro regimen often includes chemotherapy, and radiotherapy usually consists of 2 AP–PA opposed fields which cover the pelvis from perineum to the upper part of sacrum with doses about 50 Gy/5 weeks. Chemotherapy (usually mitomycin C + 5-FU) is given in cycles once or twice during radiotherapy but the importance of this remains unknown. Patients with T1–T2 tumours without lymph node involvement treated according to the Nigro regimen have a 5-year survival of about 80%, while the corresponding figure for the cases with T3–T4 tumours or lymph node involvement is 60–70% (3, 35, 44–46, 49, 57, 59, 66, 67, 72–77, 79–89). The acute toxic effects are considerable as all patients experience dermatitis/muscositis and a high percentage of the patients experience diarrhoea, general fatigue and toxic cystitis (4, 86, 91). There is, however, almost no acute mortaility and the symptoms usually disappear within a few weeks after treatment (86). Late morbidity has been observed in as much as 15% of the cases with enteropathy as the most common and serious (3, 43), but anal dysfunction, bladder dysfunction, chronic pelvic pain and fistulae are also reported (3).

The Papillon regimen usually does not include chemotherapy, and most often radiotherapy does not include the pelvic or inguinal lymph nodes. The patients receive about 30 Gy/3 weeks to a perineal and sacral field followed two months later by an iridium implant (20 Gy) into the tumour. This regimen reports a 75–80% 5-year survival regarding T1–T2 cases, while the corresponding figures for T3 and T4 cases are 60% and 5% respectively (9, 16, 40–42, 71, 73, 74, 76, 78, 90). Some of the latter patients receive APR after radiotherapy with a cure rate of about 50% (9, 42). Almost no acute or chronic morbidity is reported.

Thus, survival appears about similar for both regimens regarding small tumours (T1–T2), but the Nigro regimen appears to be preferable for large tumours (T3–T4) or when regional lymph node involvement is present. However, the Papillon regimen reports less toxicity (3, 9, 43, 78), and this regimen might be preferable for smaller tumours.

Chemotherapy

As patients now seldom die from their local relapse, the relative impact of distant metastases on survival has increased. About 20% of the patients develop distant metastases and hence have a poor prognosis (3, 73, 76, 91). Some patients with single liver metastases are cured by liver resection, and one can not exclude that very small metastases can be eliminated by intense chemotherapy followed by radiotherapy to the actual body compartment (3). However, chemotherapy has only a temporary effect

on larger metastases (73, 74, 76, 91). At present, the combination of cisplatin/5-FU appears to be the most effective, but no generally accepted standard treatment exists as there are extremely few studies on treatment of distant metastases from anal carcinoma (73, 76, 92). Adjuvant chemotherapy (5-FU + cisplatin) might be included in first-line treatment to reduce the problem of distant metastases. However, such chemotherapy involves a considerable toxicity, and only high-risk patients should therefore be included. There exists no generally accepted prognostic factors for anal carcinoma (3), but advanced tumour stage (T3–T4) and/or lymph node involvement (N1–N3) appear to involve poor prognosis (8, 46, 91, 93–95). There is a discrepancy in the literature whether histopathological grade and nuclear DNA content of the tumour might be of prognostic value (45, 82, 92, 93–96).

Follow-up

Anal canal carcinomas resolve slowly after (chemo)-radiotherapy (4, 8) as half of the tumours persists during the first few months after treatment. The great majority (80–90%) of these tumours represents only non-malignant tissue and will resolve within 6 months (4, 8). It is difficult by rectal, digital examination alone to distinguish if a persisting tumour is malignant or not. Hence, multiple core needle biopsies should be performed during this period. Approximately 10–20% of the tumours contain malignant cells and the patients must undergo APR (3). Salvage surgery (APR) must never be performed without positive biopsies. If APR is performed at an early stage of local relapse, survival is excellent as less than 10% of the patients have another relapse (3, 4, 76). The main purpose of follow-up is therefore to dignose local relapse at an early stage because an advanced, local relapse involves a poor prognosis (74, 90). Frequent digital, rectal examinations with biopsies are therefore most important during follow-up. Early diagnosis of distant metastases is of less importance as these patients seldom are cured (3, 59, 73, 74, 76, 92). Local recurrences usually appear within 3 years after (chemo)radiotherapy, distant metastases within a 5-year period (3).

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